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Disuse osteopenia: The short- and long-term effects of post-traumatic and post-surgical immobilisation following lower limb injury or total knee replacement.

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Disuse osteopenia: The short- and long-term effects of post-traumatic and post-surgical immobilisation following lower limb injury or total knee replacement.

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by

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I certify that all material in this thesis which is not my own work has been identified, and that no material has previously been submitted and approved for the award of a degree by this or any other University.

(Signature) .....

ABSTRACT

Low trauma hip fractures, due to bone fragility, are a major healthcare burden with serious consequences for individuals in terms of long-term morbidity and mortality; and also for society due to the high medical and care costs associated with these injuries. Because of the association with low bone mass, these fractures are particularly prevalent in elderly populations and are likely to become more common as longevity increases globally. Avoidance of these fractures is therefore an extremely important goal.

Low bone mass, manifested in the conditions of osteopenia and osteoporosis, is the primary cause of bone fragility, and reductions in bone mass are the inevitable corollary of aging and menopause. Bone loss may be exacerbated by immobilisation and reduced weight-bearing activity, giving rise to the condition of disuse osteopenia. Immobilisation may itself be the result of low trauma leg fragility fractures that potentially causes further bone density loss. If this loss occurs at the hip, there is an increased risk for hip fracture as a sequela to the original injury. Osteoarthritis is also a condition strongly associated with aging that may necessitate knee arthroplasty as a last stage treatment, potentially causing a period of reduced mobility and weight-bearing activity following surgery. Leg fracture and knee replacement both present additional risk factors for hip fracture due to changes in muscle mass, gait and postural stability that may increase the risk of falls.

This study aims primarily to investigate the effects of immobilisation on leg fracture and knee replacement patients, immediately following injury or surgery, in order to quantify bone and muscle loss and to monitor recovery over a one year period. A

postmenopausal population were studied as they are already losing bone density systemically and may be at greater risk of further bone loss following immobilisation. Factors of activity, function, weight-bearing, pain, treatments, therapies, health perceptions and mental wellbeing, that potentially contribute to bone loss and recovery, were also investigated. Results from the study may provide information relating to increased future hip fracture risk and lead to treatment options to alleviate bone loss in these groups.

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ABBREVIATIONS

2D	2-dimensional
3D	3-dimensional
aBMD	Areal bone mineral density
AHA	Advanced hip assessment
BMAD	Apparent bone mineral density
BMD	Bone mineral density
BMC	Bone mineral content
BMI	Body mass index
BPU	Bisphosphonate use
BS/TV	Trabecular surface density
BUA	Broadband ultrasonic attenuation
CHERC	Children's Health and Exercise Research Centre
CORIPS	Society and College of Radiographers Industry Partnership Scheme
CSA	Cross sectional area
CSMI	Cross sectional moment of inertia
CV	Coefficient of variation
DICOM	Digital Imaging and Communications in Medicine
DVD	Digital Video Disc
DXA	Dual Energy X-Ray Absorptiometry
ED	Emergency Department
FRAX	Fracture Risk Assessment Tool
FSI	Femur strength index
GAD-7	Generalised Anxiety Disorder questionnaire
GLOW	Global Longitudinal study of Osteoporosis in Women

HAL	Hip axis length
hPTH	Human parathyroid hormone
HRT	Hormone Replacement Therapy
HSA	Hip strength analysis
ICC	Intraclass Correlation Coefficient
ISCD	International Society for Clinical Densitometry
IPAQ	International Physical Activity Questionnaire
kg	Kilogram
LEFS	Lower Extremity Functional Scale
LLTM	Leg lean tissue mass
L/R WB	Left/Right weight-bearing
LSC	Least significant change
MRI	Magnetic resonance imaging
NHANES	National Health and Nutrition Examination Survey
NOF	Neck of Femur
NOGG	National Osteoporosis Guideline Group
NHANES	National Health and Nutrition Examination Survey
n.s	Non significant
OA	Osteoarthritis
OCP	Oral Contraceptive Pill
OP	Osteoporosis
PA	Posterior/ anterior
PDW SPAIR	Proton Density Spectral attenuated Inversion Recovery
PE	Precision error
PEOC	Princess Elizabeth Orthopaedic Centre

PIS	Patient information sheet
PHQ-9	Patient Health Questionnaire
PMRRC	Peninsula MR Research Centre
POP	Plaster of Paris
PTH	Parathyroid hormone
QA	Quality Assurance
QCT	Quantitative computed tomography
QUI	Quantitative ultrasound index
QUS	Quantitative ultrasound
RD&E	Royal Devon &Exeter
REC	Research Ethics Committee
RMSCV	Root mean squared coefficient of variation
RMSSD	Root mean square standard deviation
SD	Standard deviations
SOS	Speed of sound
SSRIs	Selective serotonin reuptake inhibitors
STIR TSE	Short T1 Inversion Recovery Turbo spin echo
STPE	Short term precision error
T1W TSE	T1 weighted Turbo spin echo
TBS	Trabecular bone score
TKR	Total knee replacement
VAS	Visual Analogue Scale
WB	Weight-bearing
WHO	World Health Organization
Xsect	Cross-sectional

SYMBOLS

E	Elastic modulus
µSv	MicroSieverts
GPa	Gigapascal
Z	Atomic number

CHAPTER 1. INTRODUCTION

1.1 MOTIVATION FOR STUDY

Disuse osteopenia is a condition characterized by loss of bone mineral density (BMD) and micro-architectural changes that arise as a consequence of reduced mechanical loading on the skeleton. This can be due to immobilization or lack of weight-bearing (1-5). The result of such bone density loss may be a reduction in the structural integrity of bones predisposing them to increased fracture risk. Prolonged immobilization and reduced weight bearing activity following lower limb fractures or surgical procedures may result in either unilateral or bilateral loss in BMD (6-14). The resulting effects of disuse osteopenia can give rise to an increased probability of re-fracture at the original injury site or secondary fracture at another site that has also been subject to a bone density loss due to reduced weight-bearing (15-17). This potentially includes fractures of the hip, which are more closely linked to BMD than other fracture types and have the most serious social and economic consequences due to high rates of subsequent morbidity and mortality (18). Hip fractures inevitably require hospitalization and 20% will result in patient death within a year following injury (19). A further 50% of patients will remain permanently disabled (20). Hip fracture is a serious injury of older people and as life expectancy increases globally, the number of hip fractures is likely to increase commensurately. In 2000 there were approximately nine million osteoporotic fractures worldwide and 20% of these were hip fractures (21). It is projected that on current trends in the United Kingdom (UK), there could be approximately 140,000 hospital admissions for hip fracture per year by 2036 with costs for treatment and care in excess of £6 billion (22). There is a 2.6–fold increase in fracture risk at the femoral

neck for each standard deviation (SD) decrease in BMD (23). As the rate of hip fracture increases exponentially with age, estimated to be a 17% lifetime risk from the age of 50 years in white females (18), this represents a major problem for post-menopausal women who are already losing bone systemically due to a reduction in their oestrogen levels and may be at greater risk of not recovering bone following a period of disuse.

Most research on disuse-induced bone loss is focused on spinal cord injury (SCI), stroke patients, astronauts and bed-rest volunteers and this may not be directly comparable to the effects of immobilization of a single limb (3). Earlier research on long-term unilateral disuse osteopenia is limited and the majority of studies are retrospective in design using bone density in the contralateral leg as a control. This does not account for potential residual bone deficit on the contralateral side and the full extent of bone loss in the ipsilateral leg may be underestimated as a result (11). This study affords an opportunity to assess the factors that contribute both to loss and recovery of bone mass and quality in a post-menopausal population over a period of one year, thereby identifying participants who may be at heightened fracture risk following a period of disuse. Currently there is no routine clinical pathway for BMD screening when patients sustain low trauma leg fractures as these are not considered to be strongly related to bone fragility (24). Effective and relatively inexpensive pharmacological interventions are available to mitigate bone loss (18) and prophylactic treatment, without prior screening, may be indicated for high risk groups immediately following injury or surgery, particularly when additional risk factors for osteoporosis are present.

1.2 BONE ANATOMY

1.2.1 SKELETAL ANATOMY AND FUNCTION

The human skeleton is a highly complex mechanical structure normally consisting of 206 individual bones that are grouped into two skeletal divisions: appendicular and axial. The appendicular skeleton includes 80 bones of the arms and legs together with the girdles connecting the limbs to the axial skeleton. The axial skeleton comprises the bones arranged around the axis of the body and consists of 126 bones, including the spine, ribs and skull bones (25). In combination with counter balancing forces of the body's musculature, the skeleton is capable of bearing loads in compression, tension and torsion (26). Although it primarily provides a supportive and protective framework for the body's organs and tissues, it also fulfils a number of other functions. These include:

- Insertion sites for muscles.
- Transmission of locomotive forces through the body by acting as levers for muscle contractions.
- Mineral storage, principally for calcium and phosphorus.
- Energy storage by lipids contained in the yellow marrow within bone.
- Hematopoiesis; the production of blood cells (red, white and platelets) in red bone marrow stored within certain types of bones (25, 27).

The individual components of the skeleton exhibit a huge diversity in size, shape and form, each adapted for their specific function. The capacity of bone to store energy elastically, and thereby resist fracture, is greatly influenced by shape and structure as well as by its material properties (28). Bones are classified by shape into four main types:

- Long bones are found in the appendicular skeleton and are tubular in shape designed to withstand compressive loads and bending moments without excessive deformation e.g., femur, tibia, fibula.
- Short bones are approximately equal in size in all directions and tend to have thin cortices enclosing trabecular bone. In general they are not greatly subjected to bending and primarily carry compressive loads over short distances e.g. bones of the ankle and wrist.
- Flat bones are much thinner in one direction that the other two and generally consist of two sheets of cortical bone enclosing a layer of trabecular bone. Their function is mainly protective e.g. the skull, or the provision of large areas for the attachment of muscles e.g. the scapula.
- Irregular bones have more complex shapes that partly combine the functions of the previous types e.g. the vertebrae, where the centra are load-bearing and similar to short bones whilst the projections are shaped like, and fulfil, the function of, flat bones (25, 29).

Bone is a specialised connective tissue with a composite structure consisting of trabecular bone enclosed in a layer of compact cortical bone. The typical anatomy of a long bone is shown in Figure 1.1.

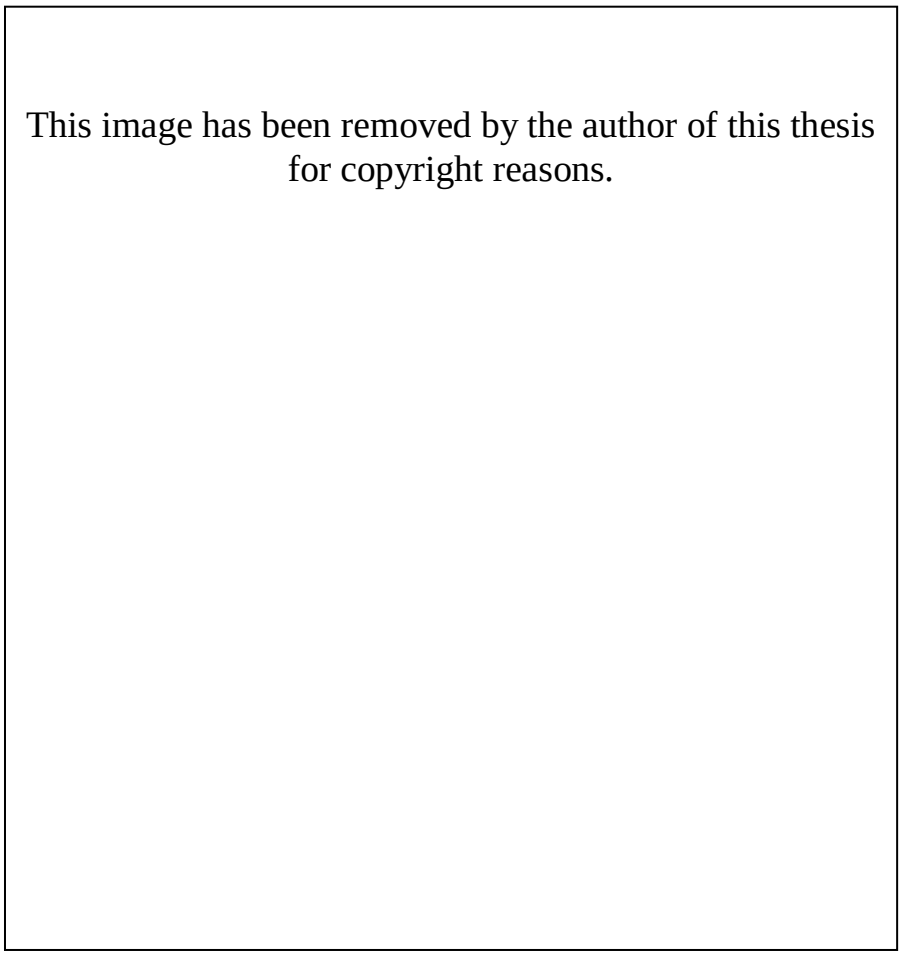

Fig. 1.1. Diagram illustrating the typical structure of a long bone (30).

Whist fundamentally the same at a nano-structural level, trabecular and cortical bone tissue have different micro- and macro-structural properties and vary in their distribution within different types of bones with trabecular bone mainly occupying the epiphyseal ends of long bones or the core of small or flat bones (31). The combination of these two types of bone and their spatial distribution within individual bones is optimized to produce site-appropriate strength and resistance to fracture (32). In a healthy condition, bone is able to continually adapt its mass and shape to the mechanical demands placed upon it. This is achieved by a process known as remodelling (27).

1.2.2 STRUCTURE AND COMPOSITION OF BONE

Bone is a specialised connective tissue having a complex hierarchical structure with the adaptive ability to regulate its structural stiffness in response to mechanical usage (33). It is a composite heterogeneous material at all hierarchical levels. The mechanical properties of bone are influenced by both material and geometric properties at any of these hierarchical levels and therefore behavioural variation is exhibited according to the composition at various skeletal sites and in differing states of age and health (34, 35). At a nano-structural level, bone has organic and mineral phases consisting of a soft organic collagen matrix interspersed and stiffened by mineral crystals of calcium hydroxyapatite (36). The organic matrix is mostly composed of the structural protein *type* 1 collagen and water (29). The collagen molecules, orientated lengthwise, pack together to form a collagen fibril. Within these fibrils are distinct gaps termed 'hole zones' and it is in these holes that the mineral crystals form (37). These fibrils, arranged in parallel, combine together to form collagen fibres which form the basis of the next level of tissue organisation (Fig. 1.2) (34).

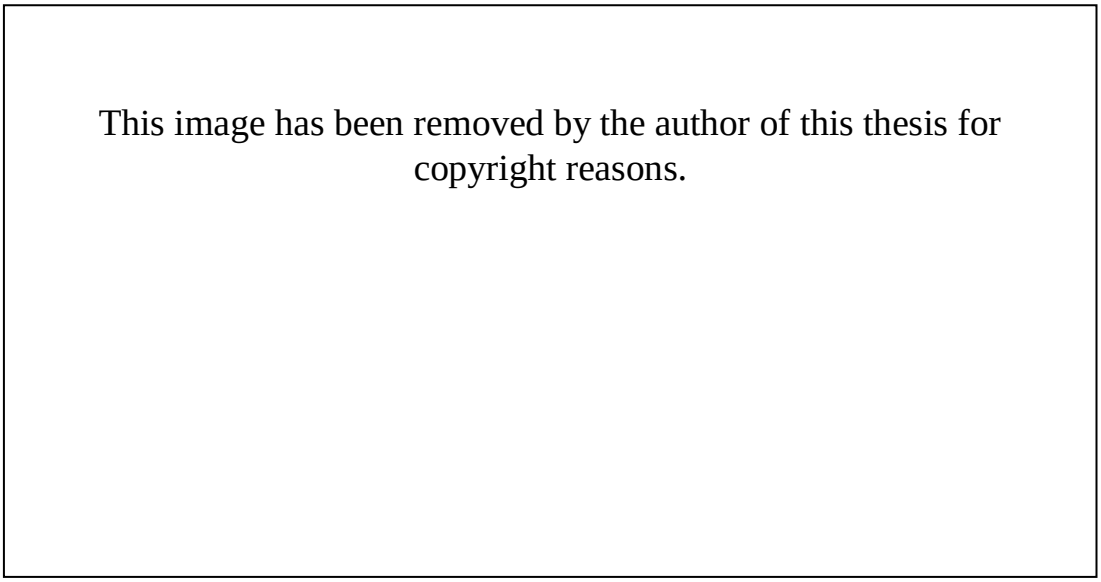

Fig. 1.2. Diagram showing the hierarchical structure of cortical bone (38)

Human bone is divided into two types; trabecular and cortical. At the nano-structural level, both types of bone are fundamentally the same (39). Beyond this level, the organisation of the tissue varies and will be discussed separately below:

Cortical (also known as compact) bone forms the outer casing of bones and defines their external proportions and geometry. Its distribution and thickness varies in different types of bones and at differing sites within bone. It has a dense compact structure with lower surface area and porosity than trabecular bone and it accounts for approximately 80% of total bone mass within the body (27, 40). Cortical bone tissue at the micro-structural level consists of collagen fibres and mineral formed into layers termed lamellae. Spaces called lacunae form between lamellae and contain osteocyte cells. The lacunae are interconnected for nutrient transfer by a system of channels known as canaliculi. Numerous lamellae, arranged concentrically, form a unit known as an osteon and many osteon units combine together, generally orientated parallel to the long axis of bones, to form the macro-structure of cortical bone. Gaps between osteons are filled by interstitial lamellae which are the remnants of older osteons. A thin layer of non-collagenous material called the cement line separates the osteon from the interstitial lamellar material (27, 34). Running along the center of each osteon is a channel called a central or Haversian canal containing blood vessels, lymphatics and nerves. The longitudinally arranged Haversian canals communicate with neighbouring osteons via a system of transverse channels termed Volkmann's or perforating canals (25, 34, 41).

Trabecular bone (also known as spongy or cancellous bone) has an open porous structure in which bony elements enclose spaces filled with bone marrow (Fig. 1.3). It is a cellular solid in engineering terms and can be regarded as a system of interconnecting

beams (trabeculae) (42). Whereas in cortical bone the collagen fibres are organised regularly in sheets of cylindrically shaped lamellae, trabecular bone consists of irregularly accreted lamellae that form trabecular elements in a combination of plate- and rod-like shapes (38). The open, porous structure of trabecular bone provides optimal strength for minimal weight and volume of material (43). Cement lines separate groups of lamellae (trabecular packets) that originate from different periods of growth and remodelling (44).

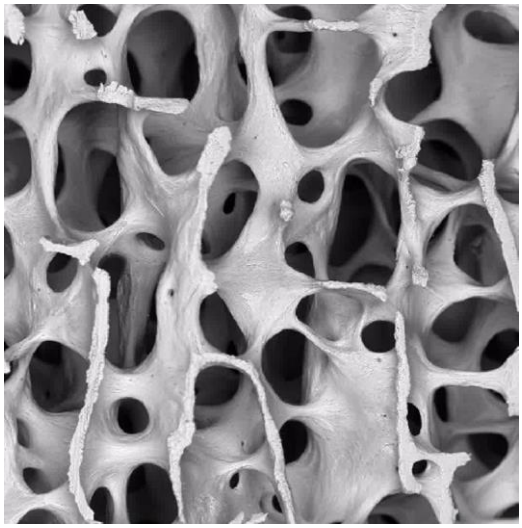

Fig. 1.3. Scanning electron microscope image showing normal trabecular bone from a lumbar vertebra (45).

The arrangement of the rods and plates is anisotropic (46). This appears to be an adaptive response to the multi-axial strains and stresses during physiological loading with the plates aligned longitudinally in the direction of principal axial loading and the rods arranged transversely, acting as stabilising links (Fig.1.4) (31, 47-49). This anisotropic alignment can be clearly seen in coronal sections and radiographs of the proximal femur (Fig. 1.5).

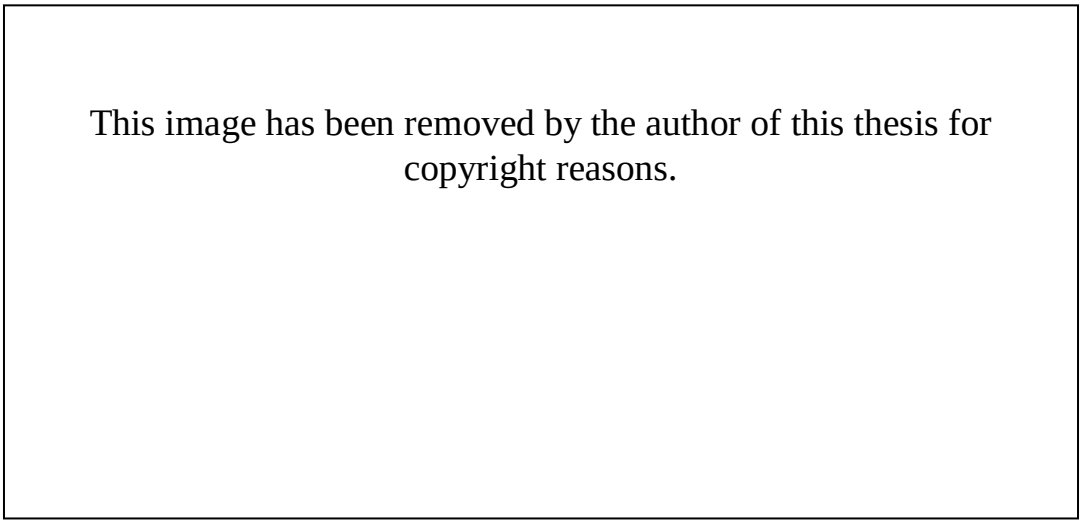

Fig. 1.4. Diagram showing principal lines of stress in the proximal femur (40)

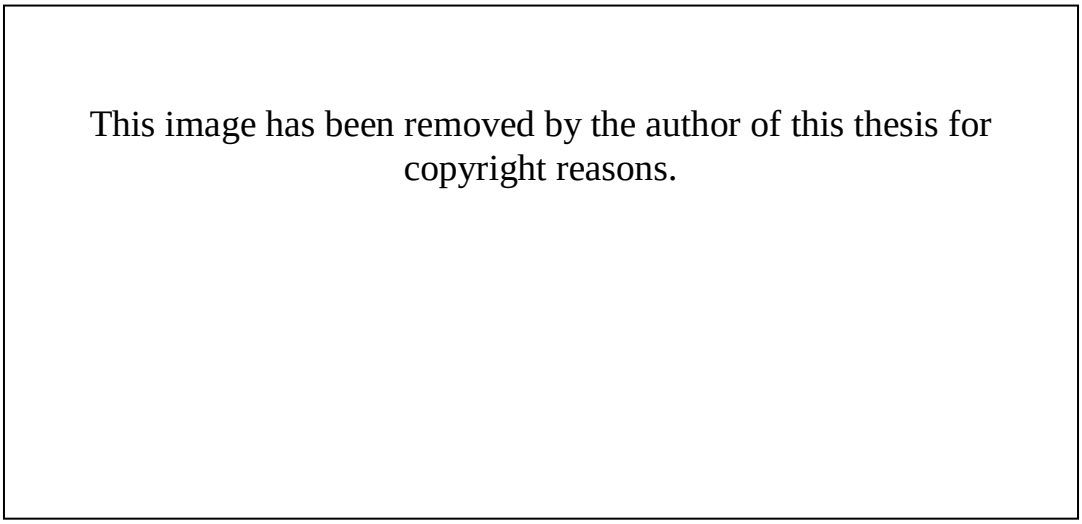

Fig. 1.5. Coronal section (a) and X-radiograph (b) of the proximal femur (50).

Trabecular bone is in general more metabolically active than cortical bone and responds more rapidly to changes in bone formation stimuli. Both the quantity and micro-architecture of trabecular bone material is therefore highly adaptable and varies widely across anatomic sites and with different age and disease states (38). In a three dimensional morphometric analysis of human bone biopsies, it was found that samples

with a lower bone mass were characterized primarily by smaller plate-to-rod ratio and to a lesser degree by thinner trabecular elements (51).

Bone marrow occupies the medullary cavity of bone and the inter-trabecular spaces. This marrow is red at birth producing both red and white blood cells. It becomes inactive yellow marrow in adulthood except in a limited number of bones that include the vertebrae and proximal femur (52).

Bone tissue has two main surfaces, the periosteum and endosteum. The periosteum is a connective tissue membrane covering the outer surface of cortical bone and contains osteoprogenitor cells and osteoblasts. The endosteum lines the medullary cavity of bones and consists of osteoprogenitor cells and osteclasts. The endosteum is further subdivided into intracortical, endocortical and trabecular surfaces. Bone is limited by its rigid non-expandable nature to appositional growth and remodelling at these surfaces. These surfaces may, at any time, be in a state of bone formation, resorption or quiescence (27).

Bone cells are categorized into four main types described briefly below:

- Bone lining cells cover the surfaces of bones. They are derived from osteoprogenitor cells and are quiescent osteoblasts (29).
- Osteoblasts are bone forming cells derived from bone lining cells and lay down the collagen matrix (osteoid) into which mineral is later deposited (29).
- Osteocyte cells are derived from osteoblasts and are located within lacunae. The cell bodies have approximately 50 - 60 long slender processes that extend into

the canaliculi and connect them to neighbouring osteocytes and bone lining cells (53).

- Osteoclasts are specialized variants of macrophage cells and are responsible for resorption of the mineralized bone matrix (54, 55).

1.3 BONE HEALTH AND MAINTENANCE

1.3.1 REMODELLING

Bone is a dynamic tissue that has the ability to maintain itself, and adapt to the physical loading placed upon it, by a continual process of bone remodelling. This process is regulated by a combination of biomechanical and biochemical factors and continues throughout life, even after peak bone mass has been achieved and skeletal growth has been completed. The adaptive process can work in both positive and negative directions such that net bone formation will result from higher than customary strains but net bone loss will follow decreased activity or 'disuse' (56, 57). Remodelling is a complex process involving the interaction of different cell phenotypes and involves the coupling of bone resorption by osteoclast cells and bone formation by osteoblasts (Fig. 1.6) (55).

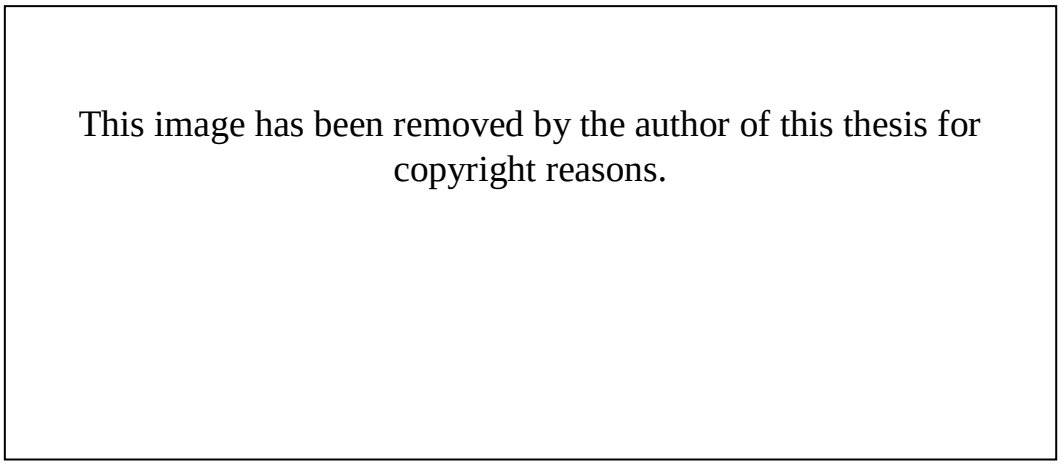

Fig. 1.6. Diagram showing the bone remodelling process (58)

Osteoclasts are multi-nucleated cells derived from haemopoietic progenitor cells recruited from bone marrow and splenic tissues. They have a ruffled border and a clear zone that serves in the attachment of the cell to bone surfaces. Bone material is dissolved by lysosomal enzymes and acids secreted by the osteoclast in the area beneath the ruffled border which forms a resorption cavity (Fig. 1.7) (59). Osteclasts have a limited lifespan and ultimately undergo apoptosis. The regulation of this programmed cell death is important in the remodelling process and can either promote or inhibit bone resorption (55).

Osteoprogenitor cells proliferate and differentiate into osteoblasts (60). These osteoblasts congregate in the resorption cavity to reform the surface as osteoid by laying down new matrix that is subsequently mineralised. As the new matrix is completed, some osteoblast cells gradually flatten to become quiescent bone ling cells whilst others differentiate into osteocytes that become embedded in the lacunae of the newly formed bone (55).

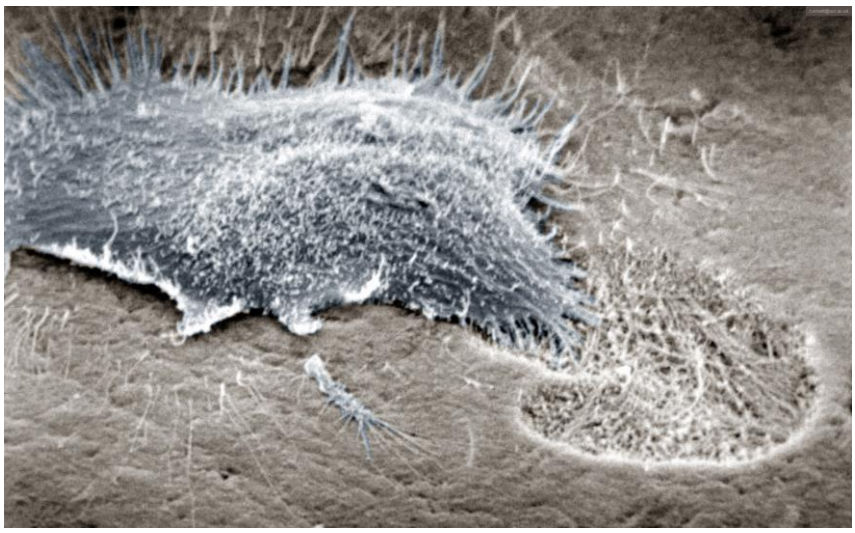

Fig. 1.7. Scanning electron microscope image of bone resorption by an osteoclast cell (61)

Remodelling occurs on endosteal, trabecular and intracortical surfaces and can change bone geometry by thinning the cortex (62). Although cortical and trabecular bone are both subject to the remodelling process, trabecular bone is more rapidly responsive to changes in loading conditions (63). Squire et al (63) found that disuse induced losses, after 21 days of hind limb unloading in mice, were two times greater in trabecular bone than in cortical bone at the distal femur and proximal tibia. Trabecular bone has up to eight times greater surface area per unit bone volume than cortical bone and as remodelling occurs on bone surfaces, those regions with higher surface area to volume ratio are susceptible to more immediate and severe bone loss (63). If remodelling is in stasis bone is maintained in a healthy condition, however an imbalance in favour of bone loss will lead to the conditions of osteopenia and osteoporosis.

The remodelling process has been known for over a century when Wolff observed the mechanical adaptation of bone tissue in response to altered functional loading and formulated his 'Law of Bone Remodelling' in 1892 (55, 64). Remodelling is controlled by a feedback mechanism known as the 'mechanostat' whereby by osteocytes sense strains caused by mechanical usage in specific directions determined primarily by the contractions of regional muscles and impact forces (62, 65). The osteocyte stimulus is locally determined and is created by displacement of interstitial fluid through the lacunar-canalicular network in which the osteocytes are located (66-68). The magnitude of the strain is communicated to the cellular network by the magnitude of the fluid shear stress (64). Mechanotransduction is the process by which osteocyte cells sense these physical stimuli and respond with biochemical signals (69). It is proposed that this operates either by direct deformation of the osteocyte cell processes projecting into the canaliculii (70) or by means of primary cilia which are solitary rigid projections

extending from the osteocyte cell body into the extracellular space. (66, 71). In vitro studies have demonstrated that shear stress induced by the flow of fluid results in the release of molecules including nitric oxide and prostaglandins that signal the remodelling response (65).

The largest forces causing strains on the skeleton arise from muscle contractions (72) and osteocyte signalling can be reduced or absent as a result of reduced mechanical loading caused by immobilization and disuse (73). Studies of bed rest in humans and hind limb disuse in rats have shown that muscle atrophy is also a consequence of reduced loading, particularly in the lower limbs, and loss of bone and muscle mass are therefore considered to be linked (74-78). Grosset and Onambele-Pearson (79) studied the time course of changes in muscle volume and shape following immobilization of the lower limbs and found rapid and substantial losses in muscle volumes distally & proximally to the immobilization site. Muscle-bone proportionality may have a bearing on the structural adequacy of bones such that a low bone mineral content value may be functionally adequate if it is proportional to regional or whole body muscle mass (62, 80, 81).

1.3.2 FACTORS CONTRIBUTING TO BONE HEALTH AND QUALITY

Although mechanical loading is the principal stimulus for the remodelling process, there are multiple biochemical factors that interact with the mechanical control of bone structure and affect bone growth, renewal and quality to some degree. The multi-factorial and interactive regulation of bone quality is highly complex. Mediating factors are broadly categorised by Davy & Hart as genetic, hormonal and metabolic as shown in Figure 1.8 (27). Pathological, systemic or local alterations to any of these factors can

lead to imbalances in the remodelling cycle and thereby cause deleterious effects on bone mass and quality (18).

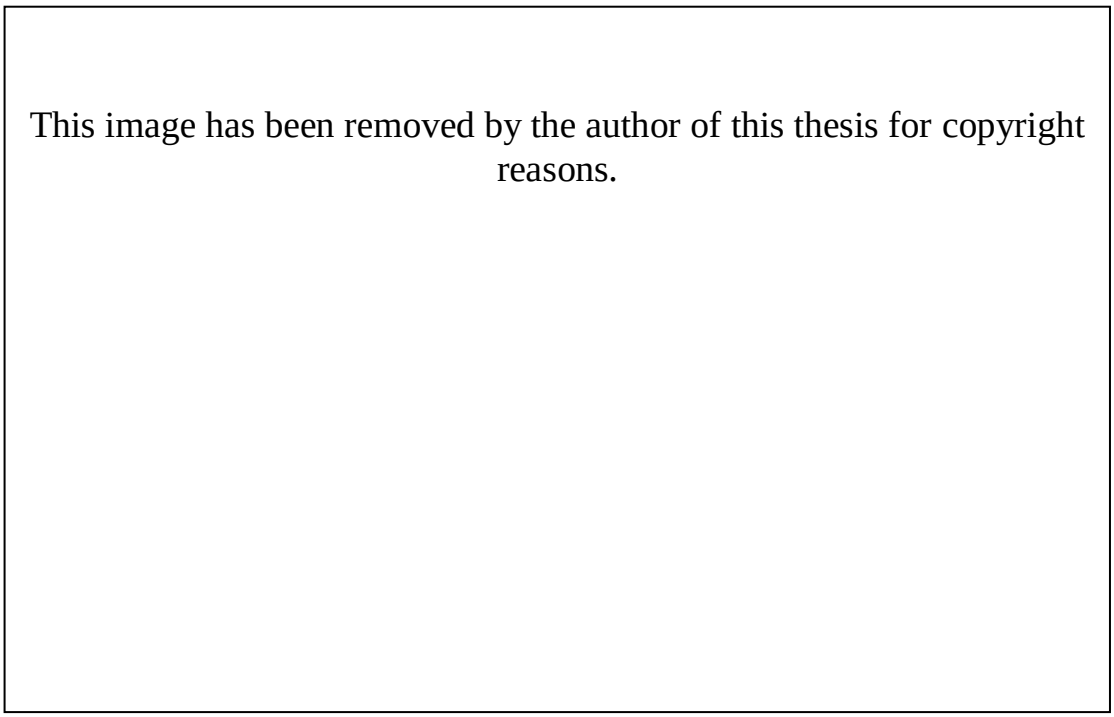

Fig. 1.8. Schematic diagram of the Davy and Hart model of the adaptive feedback process in bone remodelling (27).

The distinction between Davy and Hart's three categories of mediating factors is not necessarily clear-cut. For example, the ageing process in individuals is largely genetically controlled but can also be strongly influenced by lifestyle factors such as nutritional intake and smoking that may affect metabolism.

- Genetic factors have been widely studied in twins and families and a number have shown the heritability of spine and hip BMD to be in the range of 70-85% (2). In female populations, the ages at which menarche and menopause occur

have a genetic component and these affect the attainment of peak bone mass as a young adult as well as the onset of postmenopausal bone loss due to reduced oestrogen levels (2). Aging is also associated with a decrease in osteogenic potential (reduced osteoblast progenitor number) and an increase in apoptosis of the mechanosensing osteocyte cells (60, 82). Sarcopenia, i.e. age related reduction in muscle mass, may also have a mechanical influence on maintenance of bone mass, particularly in men (83).

Two key determinants of bone size and mass, both genetically controlled, are sex and ethnicity with average females having lower bone size and peak bone mass than average males (84). Age related declines in bone quality and quantity are different between the sexes. Dalzell et al (85) studied age related changes in normal adult radii and tibiae and found that, after the age of 50 years, declines in cortical thickness were more rapid and trabecular bone density consistently lower in females. Interestingly, they found that trabecular microstructural parameters, measured with high resolution peripheral quantitative computed tomography (pQCT), were not significantly associated with age. Chen et al found that age-related changes in cortical porosity at the femoral neck were more noticeable than changes in trabecular parameters (86). Schuit et al (87) investigated fracture incidence in elderly men and women (The Rotterdam Study) and found a similar pattern in both sexes for increasing non-vertebral fracture incidence with increasing age; however women had a higher incidence of these fractures compared to men of equal age. Differences in bone composition are evident in different ethnic groups. Asian women, for example, are reported to have lower areal BMD than Caucasian women or other racial

groups but lower incidence of hip and forearm fractures. They are also reported to have higher cortical thickness and density in addition to thicker trabeculae at the distal radius and tibia (88). Structural differences between races may not be solely attributable to genetic factors as local diet and exposure to sunlight (and thereby synthesis of vitamin D) will also contribute (89). Some cultural aspects of behaviour may also contribute to bone health; Mayhew et al, for example, suggest that the reduced hip fracture incidence in societies where near ground-level sitting is customary, may be attributable in part to a beneficial loading effect from regular standing from a squatting position (90).

- Metabolic factors that can affect bone growth and health are manifold. Maintenance of the optimal material composition of bone relies upon an adequate supply of key nutrients, without which pathological changes to bone can occur. The effects of inadequate nutrition have been observed in adolescent females suffering from Anorexia Nervosa in whom osteopenia is a frequently observed and often persistent complication of their condition (91). A range of pathological and gastrointestinal conditions such as coeliac disease, inflammatory bowel disease, chronic liver disease, chronic pancreatitis or other causes of malabsorption can inhibit the uptake of nutrients and minerals thereby exacerbating detrimental changes to bone mass and quality (18). Calcium is a major constituent of the mineral composition of bone and sufficient intake and efficient absorption is required. In addition, vitamins D and K are necessary to stabilise calcium balance and have anti-resorptive and anabolic effects (92, 93). Increased urinary excretion of calcium and decreased intestinal absorption,

leading to a negative calcium balance, are observed following immobilisation (94, 95).

- Hormonal controls modulate the functions of osteocytes, osteoblasts and osteoclasts in a systemic way (55, 62). The biochemistry and mechanisms of hormonal control in bone health encompass a vast field of knowledge and research and will not be covered expansively here. The main hormones affecting bone health are (52, 96):
    - Parathyroid hormone; produced in the parathyroid glands and regulates calcium and phosphate levels in the blood.
    - Growth hormone; produced in the anterior lobe of the pituitary gland and influences growth and remodelling of bone.
    - Thyroid hormones (T3 and T4); produced by the thyroid gland and influence skeletal development and bone mass.
    - The sex hormones, testosterone and oestrogen; influencing skeletal development and bone mass.

The contribution of hormonal controls to the maintenance of bone health is not always readily assessable. Studies of astronauts in spaceflight are conducted on optimally fit individuals who maintain a regime of exercise and controlled nutrition, nevertheless large bone losses occur due to the extreme reduction of weight-bearing in microgravity that confirms the importance of mechanical loading on bone mass. However, microgravity also affects almost all human physiological systems and it is proposed that alterations in immune and endocrine functions also play a part in this bone loss (97). A review by Sheng-dan et al. (98) observed that the pattern of bone loss in SCI differed from that

found in disuse osteoporosis. Whilst bone loss occurs in the pelvis and lower extremities of both paraplegics and tetraplegics, there is also bone loss in the upper extremities of paraplegics, who have normal innervation and weight-bearing ability in the upper limbs, indicating that hormonal influences play a part in the development of osteoporosis in these populations (98, 99). Obvious and well understood alterations in hormonal balances are observable in menopause. In addition to age-related BMD deficits, the onset of menopause brings a gradual reduction in the levels of oestrogen with consequent bone loss and changes in calcium metabolism. Average bone loss in early stage menopause is in the region of -1% per annum but it is not consistent at all skeletal sites with the rate of change at the spine showing a more accelerated, stepped decline compared to a more gradual linear decline at the hip (100).

Whilst some diseases and conditions have direct pathological effects on bone, others may have secondary effects due to hormonal changes resulting from that condition or as side-effects of medications used to treat it. Rheumatoid arthritis is a notable example where glucocorticoids are used to reduce the inflammatory symptoms of the disease but cause enhanced bone resorption alongside suppressed bone formation that can have a dramatically detrimental effect on bone mass (18). Depression is a condition that is significantly associated with low BMD (101-103) and is discussed in detail in section 1.3.3.

It should be noted that just as deficits or imbalances in hormonal, biochemical or nutritional agents can cause detrimental changes in bone health, these same agents may

be utilised therapeutically to counteract or mitigate bone tissue deterioration and will be discussed further in section 1.5.1.

1.3.3 RELATIONSHIP BETWEEN DEPRESSION, PAIN AND BONE HEALTH

Alongside the debilitating effects of depression on general recovery in activity and function following injury or surgery, depression is a condition that is significantly associated with low BMD (101-103). The reasons for this are complex and may be attributable in part to lifestyle factors, hormonal changes or to pharmacological treatments for depression (104). Depression may cause a number of behavioural responses which are risk factors for secondary osteoporosis e.g. increased smoking or alcohol consumption, poor diet and a more sedentary lifestyle that may limit exposure to sunlight with consequent reduction in vitamin D levels (105). Changes in the bone remodelling balance may be attributable in part to hormonal changes during depressive episodes including increased plasma cortisol levels resulting from stress (106). Pharmacological treatments for depression, i.e. selective serotonin reuptake inhibitors (SSRIs), have been shown to contribute to reduced BMD due to their action on the seratonin system, which is thought to have a regulatory effect on bone mass (104, 105). Depression and anxiety have been identified to have a high incidence in 1,212,413 patients undergoing total joint arthroplasty in the United States between the years of 2000 and 2008. More than one in fourteen patients had a diagnosis of depression, anxiety or both which were associated with higher healthcare costs (107).

The effects of pain and post-surgical nerve damage may also have implications for bone loss in addition to their effect on mood, mobility and weight-bearing activity. Whiteside

et al (108) report that osteopenia has been observed in humans suffering from regional pain syndrome and in a rat model of neuropathic pain. In a study of neuropathy-induced osteopenia in rats, they demonstrated a lack of correlation between BMD reduction and weight-bearing. This suggested that disruption to bone cell neurotransmission involved in the remodelling process, may also have a role in bone loss. Pain may persist for protracted periods after injury or surgery. A study of 632 TKR patients by Wylde et al (109) found that, 3-4 years after surgery, 44% of patients experienced persistent pain of a varying degree of severity, with 15% suffering severe or extreme pain. As both pain and depression can be significant problems for patients following injury or surgery, these factors merit further investigation to assess their impact on recovery and bone fragility.

1.4 MECHANICAL PROPERTIES OF BONE AND FRACTURE RISK

1.4.1 MECHANISMS OF FAILURE

It is evident that bone, as a composite structure, is highly complex and heterogeneous with varied geometric and material composition at different body sites and in different individuals. How these variations affect the mechanical behaviour and fracture potential for individual bones is an area that has been much studied over recent decades. The factors that influence the structural integrity of bone are numerous and no single factor can be regarded in isolation as the sole contributor to fracture risk.

The mechanical properties of bone include strength, stiffness and the ability to absorb energy elastically (33). The principal skeletal property with regard to weight bearing is stiffness, i.e. the relationship between load on a bone and its deformation (62). During

normal activities bones are subjected to multi-axial loading conditions in compression, tension and shear. The strength of bone in these various conditions is not the same being lowest in shear, then tension and highest in compression (48). The architectural properties of bone are necessarily a compromise and cannot be optimal for all possible loading conditions. The stiffness measured along the long axis of bone, in the direction of greatest compressive loading, is in the range of 1.6 to 2.4 times that perpendicular to the long axis. Whilst stiffness may be the main requirement to withstand loading in compression and tension, some resilience to bending afforded by elastic and plastic properties is also required. Stiffer materials are more brittle i.e. they exhibit little or no plastic deformation and fail more abruptly than ductile materials which exhibit observable plastic deformation before fracture occurs (29).

Skeletal fracture occurs where applied load exceeds strength (110). A typical load-deformation curve for bone is shown in Figure1.9. As load is applied, the material deforms in an elastic fashion whereby the material will revert to its original shape when the load is removed. If loading is sustained, the yield point will be reached where the material begins to behave plastically and will continue to deform without the ability to reform its original shape. Eventually a point is reached of ultimate stress and strain when the load is sufficient to cause total failure and a fracture will occur. The yield and failure points will clearly depend on the elastic and plastic properties of the material (33) .

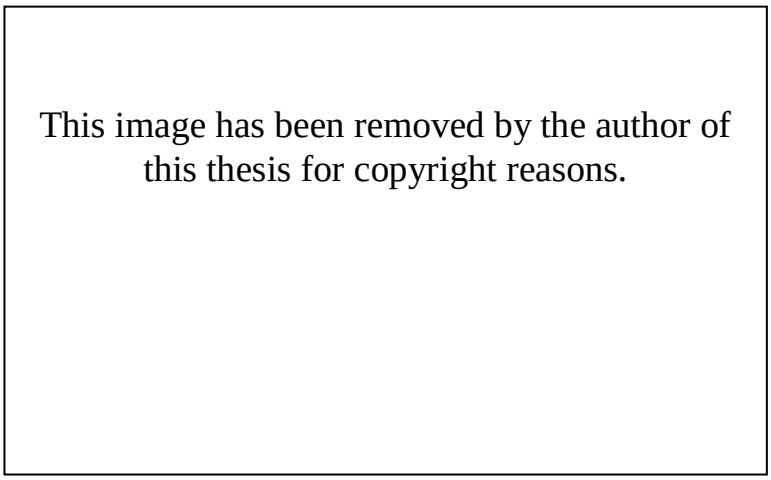

Fig. 1.9. Diagram showing the stress-strain curve of bone (111).

Stiffness, as shown in Figure 1.10, is a material's resistance to deformation given by the slope in the elastic region (112).

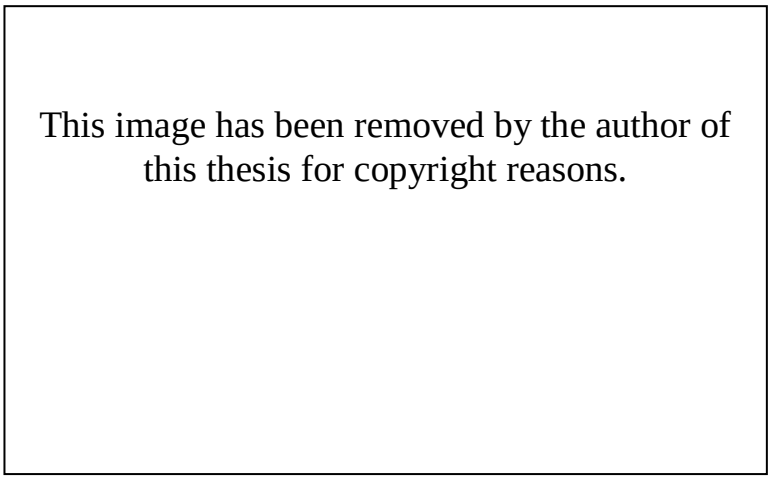

Fig. 1.10. Diagram showing the relationship of stiffness to stress and strain in bone (111).

The rate of loading is an important factor in the occurrence of fracture. High trauma incidents, such as car crashes, where very large forces are applied suddenly, will

inevitably cause catastrophic failure of bone regardless of its quality and structural integrity. Isolated overloading may not however cause overt fracture initially but repeated overloading at the same site (cyclic loading) can result in cumulative fatigue i.e. microdamage, even in healthy bone, that ultimately results in fracture at a later stage (47). Microdamage is observed in both cortical and trabecualar bone and may be present either as diffuse microscopic cracks or as complete fractures of individual trabeculae (113). It is recognised as a normal age-related physiological phenomenon but can also result from bone disorders, excessive repetitious exercise or following implantation of orthopaedic prostheses (48). Microdamage has an important role in the dissipation of energy (114) but, unrepaired, results in decreased strength and stiffness in the affected bone that may eventually lead to failure at lower loads than would be required to fracture the original healthy bone (5). It is thought that remodelling targets microdamage to prevent the accumulation of excessive damage and that this represents approximately 30% of total remodelling (115). Waldorff et.al.(5) investigated microdamage repair in a model of rat hind-limb unloading and found that, as with systemic remodelling, physiologic loading is necessary to stimulate the microdamage repair response.

Where bone quality is compromised by low density or sub-optimal structure, even low trauma events, such as a fall from standing height, can result in failure. Crack propagation and the mechanisms of mechanical failure are complex in heterogeneous materials and the mechanical properties of cortical and trabecular bone components are not the same. Susceptibility to fracture will depend upon a combination of material and geometric characteristics and, when analysing fracture behaviour, it is necessary to consider tissue properties at both a micro-architectural and at a whole bone level (33, 116).

Many studies have been conducted to identify and quantify the fracture behaviour of bone and thereby aid fracture prediction. Difficulties arise in attempting comparisons between results from such studies as the methodologies can be very varied. Lucchinetti et al (44) for example, provide a summary table of results from a variety of studies that use different experimental protocols and show measurements of the elastic modulus of trabecular material ranging between 0.76 GPa and 14.8 GPa. Mechanical testing of bone is the field of bioengineering and can take the form of macro-scale to micro-scale testing i.e. from whole bones to individual trabeculae. Problems with mechanical testing are manifold, not least because no two bone samples are identical and destructive testing can only be performed once on any given sample (117). Loading directions and the distribution of tensile and compressive stresses during a fall are complex and are not readily replicated in an experimental situation (118, 119). Additional problems in mechanical testing may arise due to variations in the preparation of samples that may have a significant effect on the mechanical properties of those samples. Bone, *in vivo*, has a variable but high water content and the hydration of test samples significantly affects their mechanical characteristics, with dry bone being stiffer and more brittle than wet (29). Removal of marrow (a viscous fluid) frequently precedes testing and this also affects the hydration of the sample, although marrow is not thought itself to contribute significantly to the mechanical behaviour of bone (29). Erroneous results may occur due to unavoidable micro-cracking damage when cutting samples or excising individual trabeculae for testing (120). By its very nature, destructive testing of bone is usually an in vitro procedure that cannot replicate the important *in vivo* muscle interactions that are determinants of load transmission across joints and of stress distribution within bones (27). Finite element analysis (FEA) affords a reproducible method to test and apply different loading conditions to generic samples created from

three dimensional computational models based on computed tomography (CT) derived data of real bone architectures (43).

The relative contributions of cortical & trabecular bone to whole bone mechanics are poorly understood and studies generally focus on either bone type in isolation (121). Reich and Geffen (122), in an *in vitro* study of the avian femur, found the deformation response and impact resistance of whole bone was substantially altered by removal of more than 10% of trabecular bone that reduced structural support and internal constraint of the cortex. Conversely, Holzer et al (123), in a study of human cadaver samples, reported that complete removal of trabecular bone from the femoral neck resulted in only a marginal decrease in femoral neck bone strength. FEA enables comparison of the mechanical contributions of trabecular and cortical components in isolation as well as their behaviour in combination. Using this method in rat vertebral bodies, Ito et al (124) calculated the yield strength in models with varying amounts of trabecular or cortical mass. They found that the mechanical contribution of the spongiosa (trabecular component) ranged between 11% and 57%. The cortical shell acted as a constraint on the trabecular material and stress was mostly distributed in the cortical shell in vertebral bodies with deteriorated trabecular microstructure. Eswaran et al performed FEA simulations of removal of the cortical shell from human vertebral bodies and found that the shell was on average only 0.38 ± 0.06 mm thick, accounted for 21-30% of overall bone mass but contributed 38-68% to overall vertebral stiffness (125).

1.4.2 MATERIAL CHARACTERISTICS OF BONE

Intrinsic variation in the material quality of bone occurs at the most fundamental level i.e. the bone matrix and the degree of mineralisation (DMB) within it (126). Mineralisation in the remodelling sequence is a two phase process of primary and

secondary deposition. Newly formed matrix starts to mineralise between 5 and 10 days following deposition but completion of secondary mineralisation is much slower, therefore older bone is more highly mineralised than newer remodelled bone (126). Higher mineralisation is associated with increased stiffness (127). Wu et al (126) investigated differences in DMB in the femoral neck cortex in women with hip fracture and demonstrated that DMB values were significantly greater in the osteons and interstitial tissue compared to controls . This result was contradicted in a previous study by Loveridge et al (128) which showed significantly less mineralisation in the femoral neck of hip fracture patients. It has been proposed that heterogeneity and a wide distribution of crystal sizes is optimal for bone strength (126) and that non-uniform inelastic deformation in heterogeneous material may enable greater dissipation of energy (129). Results from studies in this area are not always consistent and it has also been observed that hip fracture patients show greater variability in local DMB and that this variability may result in an increase in number and spread of micro-cracks (130). Busse et al (131) investigated the fracture properties of individual trabeculae and found significantly increased calcium content, decreased Young's modulus, yield strength and bending stiffness but greater heterogeneity in calcium distribution in osteoporotic bone.

Collagen itself has a major role in bone strength and toughness, and the size and arrangement of collagen fibrils affects the orientation and size of mineral crystals within it (126). Whilst the mineral phase of the bone matrix provides stiffness, collagen affords tensile strength and ductility which are major determinants of the fracture behaviour in individual trabeculae (132, 133).

Water is a significant contributor to bone mechanical properties with an inverse relationship between hydration and the ultimate stress and Young's modulus (134).

1.4.3 GEOMETRIC CHARACTERISTICS OF BONES

The mechanical efficiency of bone is not solely dependent on the quality and accumulation of material but also on the optimisation of its spatial distribution and is therefore the product of its material and geometric properties (62). The external and internal architectures of bones are both important factors in the distribution and transmission of loads, and have a significant effect on how fractures initiate and propagate throughout the material (130).

Cortical and trabecular bone both have anisotropic properties. This is manifested by the preferential orientation along the principal loading axis by the osteons of cortical bone and the plate shaped trabeculae in the spongiosa. This best adapts bone to withstand the greatest forces to which it is habitually subjected (135). Figure 1.11 shows the relative differences in ultimate stress that can be tolerated by a typical long bone in various loading directions. Kreider et al (130) discuss a study of trabecular bone samples from osteoporotic hip fracture patients that found a substantially greater orientation of bone tissue in the direction of habitual loading compared to controls with equivalent bone density. They suggest that this increased aniostrophy in these patients could reduce their ability to withstand impacts due to falls in directions orthogonal to the customary loading direction. They also report parallel findings in osteoporotic vertebrae and postulate that remodelling in osteoporotic bone may compensate for low material density by increasing anisotrophy to maximise strength in the direction of the most frequent loading.

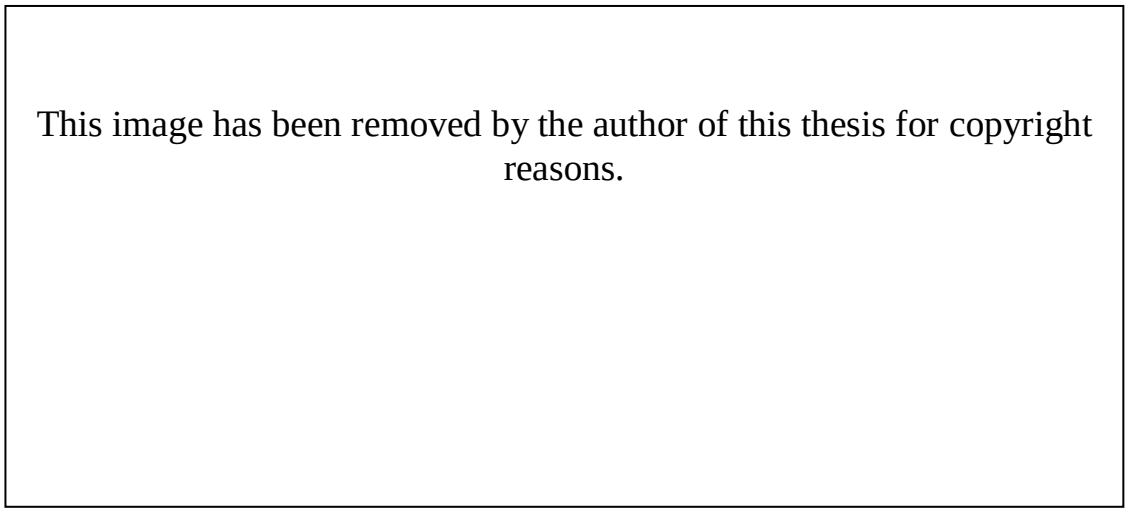

Fig. 1.11. Diagram showing the anisotropic behaviour of bone (111).

As force is applied to a material a fracture may be initiated, by debonding atoms of the material, which will propagate until the energy from that force is dissipated. The elastic and plastic deformation properties of bone are a major determinant in energy dissipation along with various geometric factors (136). Stresses in a material can be concentrated by small ‘defects’ or ‘stress risers’ such as small holes, spaces or cracks that are integral to bone tissue composition e.g. lacunae and resorption cavities (137, 138). Conversely, other structural components may serve to dissipate energy, for example cement lines. These contain minimal collagen and are less well mineralised than surrounding bone tissue thereby providing weak interfaces that may mitigate fatigue damage elsewhere by allowing cracks to occur along these lines (139, 140). The degree of porosity in both cortical and trabecular bone is a well studied area and it has been demonstrated that fracture incidence is strongly related to increased porosity (141).

The specific geometric properties of cortical and trabecular bone will be discussed below:-

- Trabecular geometry.

Optimised for strength and weight, trabecular bone has a high surface area to volume ratio that is an important factor in its potential to adapt via the remodelling process (63). Its open, porous texture can be described by a range of structural parameters that include; trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), trabecular number (Tb.N), bone surface area (BS), bone volume (BV), total tissue volume (TV), trabecular volume fraction (BV/TV), and trabecular surface density (BS/TV) (142). The connectivity of trabeculae is an important determinant of strength as more numerous, thin but well connected trabeculae are more structurally competent than an equivalent quantity of bone distributed as fewer, thicker, more widely distributed and disconnected trabeculae (138). In clinical terms, heavy reliance has been placed on the density of bone as a surrogate for bone fragility i.e. quantity rather quality. True BMD is a measure of bone mineral content (BMC) divided by volume (34). Studies that use bone density as an indicator of bone quality generally show a reduction in strength and modulus as density decreases. In a computational model, equal values of trabecular bone mass were shown to be associated with different values of biomechanical stiffness explaining how clinical bone integrity can be maintained despite significant reduction in bone mass (143). These results explain the observation that bone mass accounts for 65% of variation in bone strength whilst consideration of the full range of micro-architectural parameters may improve fracture predictability up to 94% (51).

The architectural factors that determine trabecular bone strength are interrelated in a complex fashion but the greatest mechanical competency is afforded by high

connectivity, high trabecular number and higher trabecular thickness (138) Bone loss leading to increased fragility fractures is associated with loss of trabeculae, reduced connectivity and increased inter-trabecular spacing i.e. porosity (130).

- Cortical geometry.

Whilst whole bones are recognizable by their specific shape, their mechanical properties will be affected by differences in overall size and the relative proportions of their components. Although the overall size and shape of an individual's bones is largely dictated by genetics (144) these can be modified to some degree by remodelling. Hip geometry plays a role in fracture etiology and examination of geometric factors in addition to BMD may improve identification of people at heightened fracture risk (145-147). The geometric parameters (Fig. 1.12) most relevant to hip strength are:

  - HAL: hip axis length (mm).
  - Angle of femoral neck (Θ degrees).
  - CSMI: cross sectional moment of inertia (mm^4) describes geometry and density in the femoral neck and is a measure of the distribution of material around the axis of the neck.
  - CSA: cross sectional area (mm^2) of the minimum CSMI section within the femoral neck.

These variables can be used to calculate the femur strength index (FSI) that provides an estimated ratio of the femoral neck yield strength against expected compressive stress from a fall on the greater trochanter (148).

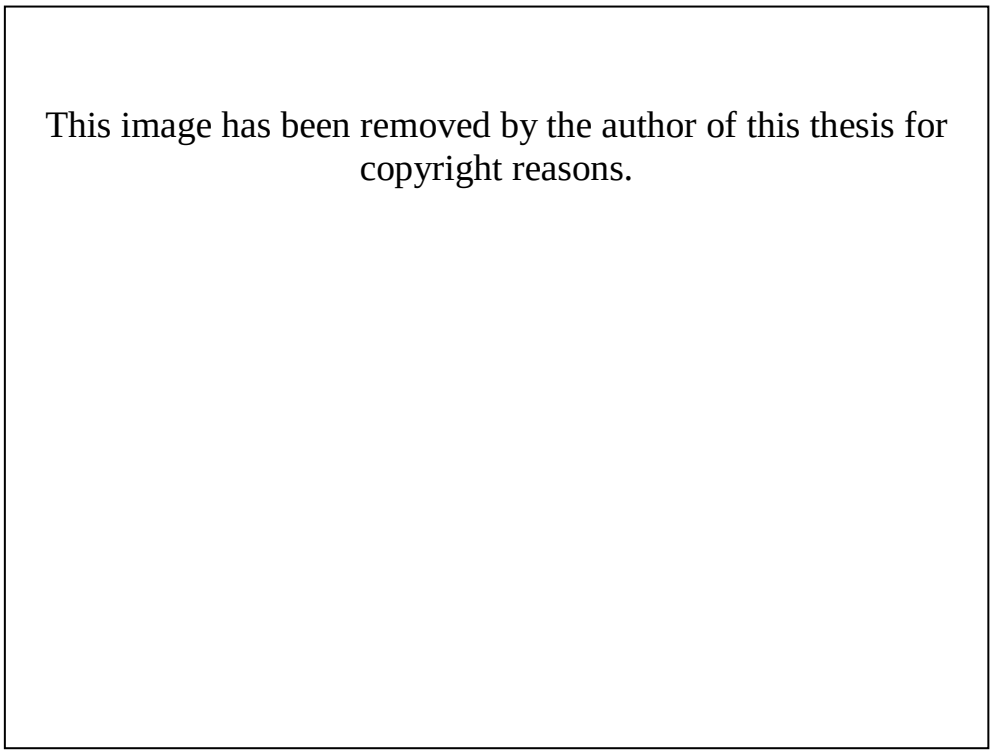

Fig. 1.12 Diagram showing geometric parameters of the proximal femur (149).

Leslie et al observed that in a cohort of 30,953 women with incident hip fractures and osteoporotic non-hip fractures, HAL and FSI made a small but significant contribution to hip fracture prediction independent of BMD and age (150). This result is corroborated by a previous study on 2506 women aged above 50 years in which HAL was significantly higher and FSI significantly lower in women with hip fracture (149).

Figure 1.13 shows the CSMI for two hollow cylinders with equal mass where one has a greater distribution of mass farther from the axis of bending (neutral axis) compared to the other. Although the walls are thinner in the right-hand structure, the distribution of material results in a substantially increased resistance to bending along its length. Larger bones have larger CSMI compared

to smaller ones and greater resilience to fracture for any given value of BMD (151). The strength and stiffness of a hollow tubular shaped bone are proportional to the product of the CSMI and the elastic modulus (E) (33). Increasing CSMI therefore increases fracture resistance if E remains unchanged.

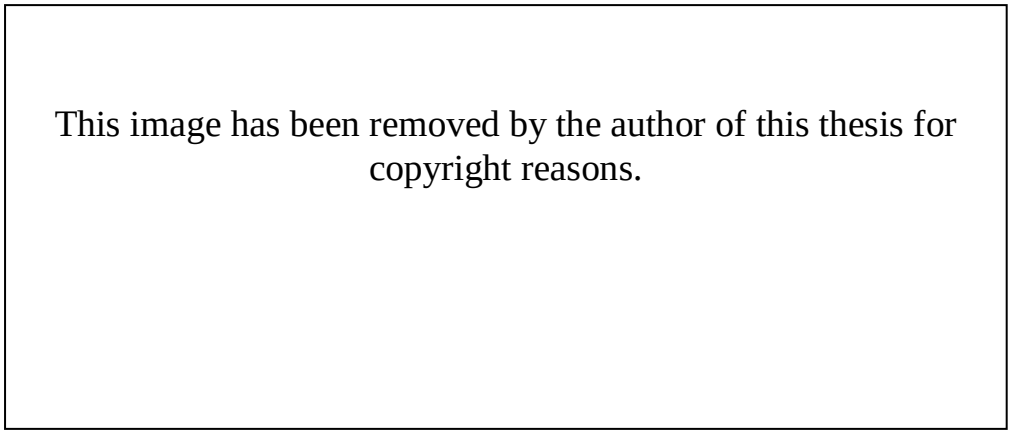

Fig. 1.13. Distribution of equal cortical mass in bones of different diameter (151).

In remodelling, expansion of long bones results from periostial apposition and endosteal resorption thereby increasing the outer cortical diameter over time. The femoral neck is an intracapsular structure not covered by periosteum. It is not therefore subject to periostial apposition and cortical thinning may consequently result (123). The potential effect of cortical thinning in the femoral neck with aging and osteoporotic conditions is an increased susceptibility to buckling fracture (152, 153). Mayhew et al (90) found that cortical thinning in this region is not uniform. Changes in physical activity with aging affect loading patterns in the proximal femur that can cause differential changes in the cortex, potentially altering its stability and exacerbating fracture risk (90). Kaptoge et al (154) concluded from a study of 7474 women, of whom 635 sustained incident

hip fractures over a period of 13 years, that the proximal femurs of elderly women with hip fracture had lower bending and CSA strengths, thinner and more asymmetric cortices, wider bone diameters and more obtuse neck-shaft angles than non-fractured participants .

Although cortical bone is relatively non-porous compared to trabecular bone, it does have intrinsic qualities of porosity that increase with age. Chen et al (86) suggest that this relates to the enlargement of intracortical channels during osteonal remodelling. Increased cortical porosity is associated with reduced bone strength, although porosity in the endocortex has less structural impact than that in the outer cortex or periosteum (138).

1.4.4 CLINICAL PREDICTION OF FRACTURE AND FACTORS RELATING TO FRACTURE RISK

It is evident that knowledge of fracture mechanics in human bone, and therefore fracture prediction, remains incomplete. Fracture in individual patients cannot be predicted with any certainty and can only be expressed as a probability extrapolated from epidemiological evidence of known fracture incidence in populations with known bone parameters. In an attempt to clinically evaluate fracture probability for individual patients, a wide range of fracture prediction tools have been designed in recent years. In current UK clinical practice the most commonly used are the Fracture Risk Assessment Tool (FRAX) & Q Fracture Scores. Based on the National Health and Nutrition Examination Survey (NHANES) database (a nationally representative sample of the United States population) (155), FRAX can be used with or without neck of femur

(NOF) BMD to estimate the 10 year probability of an individual sustaining either a major osteoporotic fracture (vertebral, wrist or humerus) or a hip fracture (156). The FRAX tool uses an algorithm that incorporates factors contributory to bone fragility including age, personal and parental history of fracture, glucocorticoid use, smoking and alcohol intake, disease and medications. Fracture risk assessment by this method is of limited clinical value without appropriate intervention thresholds at which treatment should be recommended (157). A link from the online version of FRAX to The National Osteoporosis Guideline Group (NOGG) gives some guidance to physicians in this regard (158). There are acknowledged limitations with assessment tools as they cannot take all possible risk factors fully into consideration or account for their level of contribution (159). They therefore lack sensitivity and rigid adherence to results from these tools will inevitably mean that some patients are prescribed medications unnecessarily whilst others, who might benefit from treatment, will not receive it. In real terms, fracture risk cannot be assessed on bone mechanical parameters and risk factors for fragility alone and other considerations, such as propensity for falling, need to be taken into account. This may be particularly significant for certain patient groups e.g. the elderly, recovering stroke patients, alcoholics or patients recovering from leg or other surgery where muscular control, co-ordination and balance problems may be an issue (160).

Other potential risk factors, not currently assessed in fracture risk prediction, are coming to the fore. Obesity has not been considered previously as a risk factor for bone fracture as high body mass index (BMI) has generally been associated with higher BMD. It has been suggested that fat tissue has a protective function in postmenopausal women by increasing remodelling associated with weight-bearing and possibly by cushioning against falls (161). The effects of obesity on bone are potentially complex as it is

associated with altered hormone levels including higher serum concentrations of human parathyroid hormone (hPTH) and lower circulating 25-hydroxy-vitamin D both of which influence bone maintenance and quality (162). In terms of mechanical risk, applied loads during activity can create resultant forces many times greater than during normal stance. The resultant force on the femoral head during level walking has been reported as 1.6 to 3.3 times body weight (27). Excessive stresses can be placed on bones, particularly during high impact activities, and their adequacy to support the greater loads to which they are subjected in obese people is becoming an area of increasing interest (161, 162). Skeletal alignment in obese people may also be a factor in increasing fracture risk. Alignment of the lower limb bones and joints can be substantially altered by increased soft tissue mass between the legs that compromises normal stance and gait (163). The altered efficiency of load distribution throughout the leg may potentially contribute to fracture risk.

1.4.5 FRACTURE REPAIR AND COMPLICATIONS

The healthy young body has a remarkable ability to repair bone fractures by means of callus formation and remodelling. Complications can however arise due to mal-union or non-union and as osteogenic potential decreases with aging and some disease states, fractures may not repair adequately to restore full function to all patients in these categories (164). Fracture healing is itself influenced by mechanical stresses within the callus material and early remobilisation may mitigate bone loss elsewhere due to the effects of limited weight-bearing. Nevertheless, to prevent re-fracture, an appropriate degree of healing and restoration of stiffness must take place before full weight-bearing and return to normal gait is attempted (165, 166). Some of the major and life-

threatening consequences of fracture are not related to the repair process but result from postoperative medical complications such as cardiac or pulmonary problems. These outcomes are frequently associated with fractures of the hip and account for the poor recovery and high mortality rates following hip trauma (167).

1.5 BONE DISEASES AND DISORDERS

Disruptions to the mechanisms that control skeletal growth and maintenance have potential to cause a wide variety of bone diseases and disorders either by directly affecting bone tissue or indirectly by interfering with mineral metabolism (168). Osteoporosis (OP), osteopenia and osteoarthritis (OA) are common degenerative conditions in aging populations & will be discussed in the following sections.

1.5.1 OSTEOPOROSIS AND OSTEOPENIA

Osteoporosis is defined as a systemic skeletal disorder characterised by a reduction in bone mineral density and micro-architectural changes that increase bone fragility and susceptibility to fracture (169). Osteopenia is a precursor of OP but is not regarded as a disease state. OP may be either ‘primary’ or ‘secondary’. Primary OP is the most common form and is not caused by another disorder whereas secondary OP arises as a consequence of other specific diseases or medications that affect the bone remodelling process. Primary OP is mainly age-related although idiopathic forms can occur in younger people. Whilst genetics, nutrition and a range of lifestyle factors influence age related bone loss, oestrogen deficiency is common to men and women and is responsible for the gradual phase of bone loss in both. OP is however 2-3 times more prevalent in females mainly due to the accelerated phase of bone loss lasting between 4-8 years around the time of menopause. It is an asymptomatic condition until physical

changes manifest themselves as reduced height, altered stature and low trauma fractures that can result in pain and disability (168). It is therefore often described as a silent disease and may be frequently undiagnosed and untreated even after an event causing low trauma fracture(170).

In 1994 the World Health Organization (WHO) formulated a simplified stratification of BMD values to define OP. The categories are based on standard deviations from the young adult mean BMD i.e. T scores, and are: normal (T score > -1), osteopenia (T score -1 to -2.5) and osteoporosis (T score < -2.5). These categories have been taken to represent a fracture risk of low, medium and high respectively (21). There is an exponential relationship between fracture risk and T score as shown in figure 1.14. In this figure (approximating to the relationship between hip BMD and hip fracture risk), fracture risk is increased by a factor of 2.5 for each unit T score reduction, therefore a relatively small reduction in BMD in the osteoporotic range can substantially increase the probability of fragility fracture (171).

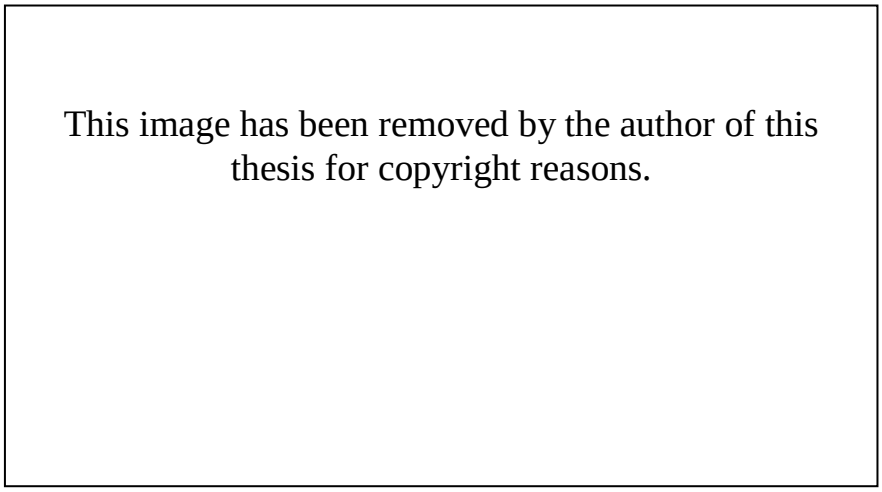

Fig.1.14 Graph showing relationship between T-score and fracture risk (171).

Using the WHO criteria, approximately 20% of postmenopausal women in western countries would be diagnosed as osteoporotic (169). Although T scores provide a useful framework to assess potential fracture risk, it is well recognised that BMD only explains

part of bone fragility and a large overlap exists in low trauma fracture incidence across the BMD categories (172).

- Disuse osteopenia

Static weight-bearing, ground reaction forces and mechanical loading generated by muscles during locomotion are important physical stimuli for bone remodelling (173) and it is axiomatic that immobilization and an absence of load-bearing will result in a reduction in BMD as manifested in the condition of disuse osteopenia. Disuse osteopenia is a secondary form of osteopenia/osteoporosis that can occur at any age and has been observed in human studies of bed-rest (74, 174, 175), SCI (176), stroke (177-179) and conditions of micro-gravity (180-182). Bartl and Frisch (4) report that young bed-ridden patients can lose up to 30% of their bone density in only a few months and that on average there is a decrease in trabecular bone of approximately 1% per week but only a 1% per month recovery on resumption of physical activity. The effect of lack of weight bearing on otherwise healthy & physically active human subjects is most clearly demonstrated in studies of astronauts following time spent in microgravity during space missions. Lang (110) reported that up to 15% of bone strength can be lost at the proximal femur over a 6 month flight. Zayzafoon et al. (183) state that in the most severe forms of bone loss due to micro-gravity, there is a 2% decrease in BMD in a one month period equating to that of a post-menopausal woman over the period of one year. Immobilization induced bone loss has generally been found to be greater at the epiphyses (where trabecular bone is most abundant) than the diaphyses. This has led to the assumption that bone loss is greater in trabecular

compared to cortical bone. More recent evidence contradicts this assumption showing that bone loss in the distal tibial epiphysis after 35 days of bed rest was predominantly from the cortical compartment (72). Although both human & animal models of disuse osteopenia exhibit similar responses to reduced weight bearing, intriguing evidence has emerged from studies of hibernating brown bears (Ursas Americanus) that demonstrates minimal bone loss during protracted periods of hibernation inactivity. This suggests that some mechanism of hormonal or biological control may be able to mitigate the effects of disuse to a major degree in these mammals (97, 184-186).

There is a large body of literature on the subject of disuse osteopenia and studies include both *in vivo* and *in vitro* human and animal models at various skeletal sites. Methods of measurement, including Dual Energy X-Ray Absorptiometry (DXA), Quantitative Computed Tomography (QCT) and high resolution Magnetic Resonance Imaging (MRI), and the parameters of bone quality measured are varied. Mechanical assessment includes histomorphometry, FEA and mechanical testing of tissue samples. These studies mostly focus on trabecular or cortical bone in isolation and few consider the combined effects of both. The diverse methodologies employed in these studies each have their own limitations and direct comparison of results is not always readily made.

There are major differences in the extent of skeletal weight bearing at different sites within the body. Other than the patella, bones of the lower extremities are subject to the highest loads. Fracture or injury to the lower extremities is therefore likely to result in the greatest loss of bone following disuse (11).

Jarvinen and Kannus (11) provide a comprehensive review of studies, up to 1997, of injuries to the lower extremities and their effect on bone density. The studies are grouped into knee injuries, femoral shaft, tibial shaft and ankle fractures. It is evident from all of these studies that varying degrees of bone loss are associated with lower limb injury. This also includes bone density changes in the contralateral limb. Several studies include measurement of BMD changes in the proximal femur (6-9, 12, 187). These studies, with one exception (8), showed long-term bone loss in the ipsilateral proximal femur to a varying degree as a result of lower limb injury. The length of follow up period and the sample populations, in terms of age and sex, varied greatly in these studies. In each case the sample size was very small, maximum 29 participants. The majority of these studies were retrospective in design and compare bone density on the affected side against the contralateral limb i.e. effectively using this as a control. If this assumes that no or minimal bone loss has occurred in the contralateral limb post injury, calculation of the relative difference between ipsi and contralateral sides may considerably underestimate the absolute loss in the ipsilateral limb after the baseline injury.

- Time course of bone loss and recovery

Post traumatic bone loss is a high turnover condition whereby both formation and resorption of bone are increased but out of balance such that the later is greater than the former. The most important determinants in the development of disuse bone loss appear to be the length of immobilization and impairment of function. The time span of recovery is greater than the duration of the unloading that caused the bone loss (9, 11). Ito et al (188) found that bone in the trabecular

and endosteal regions diminished faster and recovered more quickly than the cortical compartment in a study of tibial BMD in patients with hip surgery. A study by Van der Wiel (9) found that bone loss in the proximal femur following unstable leg fracture showed no sign of recovery in the trochanter and femoral neck after one year. In a study of bone loss following unilateral tibial fracture, Eyres and Kanis (189) found that persistent bone loss remained in the distal tibia, at a mean time interval of 8 years post fracture, for patients who had sustained their fractures during adulthood; no significant differences in BMD were however apparent in the injured and control limb after fractures sustained in childhood. In a case study of prolonged external fixation of a severe tibia/fibula fracture, Knapp et al (13) found that the patient demonstrated a T-score 2.5 standard deviations (SD) lower on the ipsilateral hip 18 years after the original injury. In a computational model of disuse, restored trabecular architecture was found to differ from the original and the duration of the osteopenic stage was found to be the main determinant of these changes. Older individuals may have diminished osteogenic potential with fewer trabeculae acting as a scaffold for new bone formation and thus may be least likely to recover bone mass after disuse (143). These findings have clinical implications and strategies to reduce the period of unloading may be indicated to alleviate bone loss. Factors such as type of medical treatment, levels of pain and depression that delay remobilization and restoration of normal activity levels may also contribute to the degree and time scale of recovery (11).

- Treatments and therapies

Although bone recovery to baseline values has been reported in some studies following re-ambulation or return to normal gravity (98), in most instances of disuse osteopenia, recovery is slow and incomplete. There are however interventions, including lifestyle and nutritional changes, that can either reduce bone loss or contribute to its recovery (190). A range of therapeutic agents are available that have varying effects on bone turnover and the matrix properties, mineralisation and microdamage accumulation in bone. These may be either antiresorptive or anabolic and can have different effects in trabecular and cortical bone (169). Bisphosphonates are a range of antiresorptive drugs including Etidronate, Alendronate and Risedronate. These are selectively distributed to bone where they inhibit osteoclast activity and shorten their lifespan. Anabolic agents directly increase bone formation and are a less well developed group of drugs that includes parathyroid hormone (PTH), sodium fluoride and strontium ranelate (18). Bisphosphonates including tiludronate have been demonstrated to be an effective treatment in paraplegic patients (98, 191) and alendronate has been shown to be both well tolerated and effective in non-ambulatory children (192). Trabecular bone increases in the tibiae of immobilized rats treated with 1,38 hPTH were reported in a study by Ma et al (193). Nutritional interventions have been reported to have a small influence in rectifying the negative calcium balance in disuse osteopenia (92).

New data suggests that muscle contractions may prevent disuse osteopenia independent of weight-bearing and therefore, where safe and practicable, strategies to return patients to early resistance exercise may be useful (194). Grosset and Onambele-Pearson (195) postulate that for certain injuries the use of

a removable splint would enable patients to exercise and limit the process of atrophy. It has been suggested that the shivering of skeletal muscles in hibernating black bears may contribute to the maintenance of bone mass during hibernation by a mechanism involving low magnitude mechanical stimulation (184) and non-pharmacological therapeutic interventions such as vibrating plates (196) may have a role in bone recovery.

1.5.2 OSTEOARTHRITIS

OA is a disease that can involve peripheral and axial joints and is most common in the knees, hips and hands. It arises from a repair response to tissue damage caused by wear or trauma and although aging itself is not a cause of OA the condition is nonetheless strongly associated with advancing age. OA is a metabolically active process that repairs damaged tissue by structurally altering the joint and can be symptomless. However, this repair process may be compromised resulting in localised cartilage loss and structural alteration of the adjacent bone, ultimately causing joint pain and limiting function (197). As both OA and osteoporosis (OP) are age related, it might be expected that the two conditions would regularly co-exist in elderly populations. Research over recent decades has generally demonstrated a higher bone mass associated with OA and therefore the two conditions have been assumed to be mutually exclusive (198, 199). A study by van Hove et al, investigating osteocyte morphology in human tibial bone from different pathological states, observed significant differences in OA and OP affected bone suggesting that the two conditions are quite distinct (53). More recent research indicates that the relationship between OA and OP is more complex than originally proposed (200). Glowacki (199) reports that several studies using DXA assessed BMD, demonstrate an incidence of occult OP in 20-29% of both men and women with OA. A

study by Drees et al (201) found that in 82 osteoarthritic, postmenopausal females, (who subsequently required knee or hip replacement), 23.2% were affected by OP reflecting the normal distribution of OP in the general female population. Although higher BMD is part of the pathogenesis of OA, this potentially disguises poorer quality of sclerotic bone and inferior fracture resistance. Osteoarthritic bone has thicker trabeculae than normal or osteoporotic subchondral bone. It is also characterized by increased subchondral plate thickness, osteophyte formation, and the development of bone marrow lesions that may precede the formation of bone cysts. It has been generally thought that osteoarthritic subchondral bone is stiffer and therefore more brittle than normal bone, but more recent work suggests that remodelled bone in OA is less mineralised and therefore less stiff. These characteristics have also been found in the inter-trochanteric region of the proximal femur, some distance from the subchondral region, suggesting that pathological changes in OA are not restricted to the subchondral bone (202). Localised osteosclerosis in hip OA sufferers may manifest itself as higher BMD that does not reflect bone density status elsewhere in the body. As the femoral neck region of interest (ROI) is generally used for fracture prediction, errors may result if this ROI is considered in isolation.

Arden et al report evidence from large population studies where levels of BMD are up to 15% higher in OA patients compared to controls (203). As increased BMD is generally associated with reduced fracture risk it might also be expected that OA patients would demonstrate reduced fracture prevalence; a number of studies indicate that this is not the case (203-206). The reasons for this are not clear but may be attributable to a variety of functional impairments associated with OA that possibly contribute to an increased propensity for falls and greater severity of injuries. These

include reduced agility, reduced muscle strength, postural instability and heightened pain levels (203, 207). In addition to causing a general impairment in activity levels and function, OA also commonly necessitates joint replacement with limited and impaired mobility for a variable period post surgery (208, 209). A study by Prieto-Alhambra et al (210) showed that patients with knee OA, from the General Practice Research Database (UK), have a non-significantly lower hip fracture incidence than controls in the year preceding total knee replacement (TKR), but a significantly increased hip fracture incidence in the year following surgery (RR 1.58; 95% CI) that only returns to the same level as the control group 3 years post-operatively. These results were supported by a further study using the Dutch PHARMO Record Linkage System (211). Whilst the authors discuss the aforementioned possible reasons for this phenomenon (propensity for falls etc), the extent of disuse-related bone loss at the hip following TKR and its potential contribution to post-surgical hip fracture risk has not been reported. Bone loss at the tibial and femoral diaphyses has been demonstrated following TKR and this was most marked in the operated leg for one year post-operatively (212). Post-surgical bisphosphonate use (BPU) has been found to be associated with a 50-55% hip fracture risk reduction in a TKR population (213). As BPU would be expected to alleviate the effects of disuse-related bone loss, this finding supports the suggestion that post-surgical disuse may indeed play an important contributory role in hip fracture following TKR (214).

1.6 IMAGING TECHNOLOGIES FOR THE QUANTITATIVE EVALUATION OF BONE AND SOFT TISSUE

BMD measured by DXA is currently the primary screening tool for clinical diagnosis of osteopenia and osteoporosis but has limitations because of the large overlap in the

BMD of patients who do or do not sustain fractures (215). Sornay-Rendu et al (216) showed that 48% of women who sustained a fragility fracture had a baseline BMD in the osteopenic range and 8% were in the normal range. A combination of structural and densotomic indices can provide a more accurate assessment of bone quality and fragility that may improve sensitivity and/or specificity to identify individuals at heightened fracture risk (51). Bone structural parameters are not however currently assessed as part of normal clinical routine.

Much of the current knowledge of the mechanisms of bone failure comes from computational and theoretical studies based on data derived from 3-dimensional imaging modalities (217). High resolution QCT (33) and high field 3-Tesla MRI (218) can provide information non-invasively regarding mass, volumetric density and distribution of mineralised tissue and these are valuable research modalities for *in vivo* assessment of bone architecture. In an *in vitro* study by Bousson et al (219), the combination of QCT densitometric and geometric variables in the proximal femur explained 76% of femoral failure load variance compared to 69% explained by DXA BMD. Whilst the last decade has seen considerable progress in bone imaging techniques, there are major limitations to their use in clinical situations due to low availability, high cost, inconvenience for patients and, in the case of CT, higher radiation dose (220). Quantitative ultrasound (QUS) affords a relatively cheap option to provide densitometric information from either Broadband Ultrasonic Attenuation (BUA) or Speed of Sound (SOS). Some systems combine BUA and SOS to provide a single measure of bone density: the Quantitative Ultrasound Index (QUI). QUS offers a fast, safe and convenient option for patients in that it measures peripheral sites, usually the calcaneus, and does not use ionising radiation (171).

1.6.1 DXA

DXA is, at present, the most widely used, non-invasive, modality for *in vivo* research and clinical assessment of BMD and the quantitative evaluation of soft tissue. DXA may be used to measure BMD at any skeletal site but it is typically used to measure posterior/anterior (PA) lumbar spine and the proximal femur as these are the most clinically relevant in terms of fracture incidence and severity (221). DXA is a 2-dimensional (2D) modality that utilises the differential attenuation of X-rays with two different photon energy peaks, by bone and soft tissue. The attenuation of X-ray photons in a given material allows the areal density (mass per unit area) of that material to be calculated. The attenuation coefficient of any material is dependent on its atomic number and the photon energy of the X-ray beam transmitted through it. Simultaneous scanning with two beams of different photon energy enables acquisition of high- and low-energy profiles of tissues in the scan line. Low-energy photons are attenuated slightly more than high energy photons in soft tissues. The attenuation differential between the two photon energies is greater in bone because it has a much larger attenuation coefficient at lower photon energies than soft tissue. In a two dimensional image of the body there is soft tissue over- and underlying bone and subtraction of the high-energy from the low-energy profile is used to provide information on variation in BMD along the scan line (221). Soft tissue regions immediately adjacent to bone are used as a baseline reference area for soft tissue composition when calculating the differential between the two energy profiles in the in the ROI. The attenuation coefficient of fat is different to that of lean soft tissue due to its higher hydrogen content and the same principle of differential attenuation between tissue types is used to derive information on tissue distribution in DXA total body scans (171). Data from total body

scans therefore allows determination of the proportionality of muscle and bone mass, either for specific regions or for the body as a whole (222). DXA methodology is based on the differential attenuation between two tissue types and is only strictly accurate when that condition applies (223). Soft tissue in the ROI will invariably contain a combination of fat and lean tissue therefore differences in the soft tissue composition i.e. lean/fat ratio, in the path of the X-ray beam compared to the adjacent reference area, may cause errors in the accuracy of BMD measurement (171).

As a 2-dimensional imaging technique, DXA can only calculate areal BMD (aBMD) which only provides a surrogate for true BMD (mass per unit volume) as measured by 3-dimensional (3D) techniques. Because aBMD does not have a value for depth, misleading values are obtained where the projected area is either much smaller or larger than average for any given ROI. This anomaly may be minimised by correcting for the missing depth value to provide an estimate of 'apparent' BMD (BMAD) (224, 225).

DXA has stable calibration and high precision (221) but a number of issues should be considered when interpreting results from repeat scans:

- As biological changes in BMD are generally small relative to the error inherent in the test itself, interpretation of serial BMD tests depends on knowledge of the least significant change (LSC) in BMD that is beyond the range of error (226). In clinical terms, significance is based on a LSC of 2.8% assuming precision error of 1% (227).
- Higher BMI has been demonstrated to contribute to increased DXA precision error due to a reduction in signal to noise ratio in larger

participants (228). In addition, tissue inhomogeneities may be more evident in these participants. These inhomogeneities may alter over time as a participant's weight and muscle mass fluctuates, changing the distribution of soft tissue in the ROI and resulting in long-term precision error (229).

- Variation in a participant's positioning for repeat scans can cause measurement error and it is therefore desirable to use the same operator to avoid inter-operator differences in positioning technique. Participants may also change in their ability to assume correct scan positions over a prolonged period of follow-up particularly if they suffer from degenerative musculo-skeletal conditions that affect their flexibility. This is notable in scans of the hip where internal rotation of the legs is required to achieve the correct scanning position (230).

DXA also has limitations in that it does not distinguish between cortical and trabecular bone. It is therefore unable to provide specific information on how these two different bone types respond to external stimuli and treatments for osteoporosis (219). Despite these limitations DXA is currently the gold standard methodology for clinical diagnosis of osteoporosis on the basis of its relatively low cost, availability and convenience for patients, short scan times and minimal radiation dose (171). The effective radiation dose for a PA spine examination using DXA is typically in the region of 1.0 microSievert compared to 60 microSieverts for QCT in an average sized adult participant (231). The advantages of DXA, particularly for research purposes, include a number of recent technological developments that could be potentially incorporated into clinical routine to complement BMD information and enhance fracture prediction.

- The macro-scale geometric parameters of the hip, and their relevance to the mechanical properties of the proximal femur, have been discussed in section 1.4.3. Advanced Hip Assessment (AHA)/Hip Strength Analysis (HSA) software is available commercially and can be used during routine hip scans to provide geometric measurements of the proximal femur. The structural parameters measured can be combined with age, height and weight to calculate the femur strength index (FSI) as an ancillary measure of hip structural competence (149, 156). Whilst HAL and FSI have been demonstrated to make a small but statistically significant contribution to the prediction of hip fractures, the incremental information gained from this analysis may be too minimal to justify its use in routine clinical practice except in borderline cases (150).

- The known limitations of standard densitometry have been a driver for the development of techniques to assess bone microarchitecture. Although methodologies, such as high resolution QCT and MRI, have the capability to provide this information, their use is not practical in clinical situations. Boehm et al (232) investigated the topological properties of bone mineral distribution patterns from images generated during conventional DXA hip scanning to test the ability of this method to discriminate between postmenopausal women with hip fracture and controls. In a study population of 100, of whom 50 were hip fracture patients, they found 71-84% of patients were correctly identified by regional topological analysis compared to 58-68% identified by BMD. Using a similar principle, based on two dimensional DXA image analysis, software has recently been developed to provide a Trabecular Bone Score (TBS, Med-Imaps, France) for assessment of the lumbar spine ROI. TBS is a grey-level texture

measurement that differentiates between two micro-architectures exhibiting the same bone density but different trabecular characteristics (233). A study by Boutroy et al (234) assessed 564 postmenopausal women over a mean follow-up period of 7.8 years during which 94 sustained a fragility fracture. They concluded that BMD and TBS predicted these fractures equally well but a combination of the two indices afforded only limited additional information on fracture prediction across the entire cohort. Nevertheless, they found that a subset of women in the osteopenic range of BMD with lowest TBS were at higher risk of fracture. Further *in vivo* research on the efficacy of TBS to predict fracture would be valuable.

1.6.2 MRI

MRI is a non-invasive 3D modality that can produce images in various planes. It is a highly complex technology that utilizes magnetic fields and radio waves to construct images mathematically (230). MRI exploits the magnetic properties of the abundant hydrogen atoms in body tissues. Hydrogen atoms have one proton in the nucleus and effectively behave as mini magnets. In normal conditions, these protons spin on their axes and precess in a random fashion. In MRI, magnetic fields are employed to alter this random orientation and spin of the hydrogen protons. Energy, in the form of radio wave pulses at a particular resonant frequency, is introduced to the system and absorbed causing the hydrogen protons to precess in phase. As different tissues contain varying quantities of hydrogen, energy absorption will vary accordingly (235). When energy transfer ceases, the hydrogen protons ‘relax’ returning to a more random configuration and energy at the same frequency is reemitted. This produces signal that can be interpreted mathematically to produce an image. The rate of relaxation in different

tissues, generally referred to as T1 or T2, affects the image appearance whereby different brightness properties are exhibited by tissue type according to which relaxation mode is applied (230).

MRI is regarded as a safe technique to image bone and soft tissue that does not employ ionising radiation. Because soft tissues have high hydrogen content due to their composition of approximately 85% water (H_2O), MRI is an excellent imaging modality for soft tissue anatomy. Whilst bone itself does not produce a signal in MRI, due to the tightly bound hydrogen nuclei within the bone matrix (230), its structure can nevertheless be inferred from the negative image created by the strong signal generated in abundant fat and water in the surrounding soft tissue and marrow (220).

The description of MRI given above is extremely simplified and the parameters that can be manipulated to affect image quality will not be addressed in detail. Image quality depends on the amount of signal produced and this is influenced by data acquisition time, field strength, and the pulse sequence and echo time used (220). In common with any imaging technology, image quality is dependent on the resolution that can be achieved by the system. Smaller voxels contain fewer hydrogen atoms and produce lower signal than larger voxels. Higher resolution is achieved by increasing signal accumulation and this demands higher energy input to the system. This is associated with heating effects and is therefore a comfort and safety issue for the participant being scanned. High resolution *in vivo* imaging involves a compromise between minimising heating effects (by increasing exposure time) and producing artefacts that inevitably result from patient movement as the scan time increases. This is a major limitation of MRI to image fine structural detail *in vivo*. Trabeculae are typically in the range of 80-

150 microns in diameter, below the minimum spatial resolution achievable in most systems (236). MRI systems, commonly 1.5 Tesla, used in clinical or research practice do not have the capability to produce *in vivo* images of bone microstructure, however using a higher field strength will increase signal and reduce exposure time; high resolution 3 Tesla MRI scanners have been used for this purpose in a research context (218). Super-high field strength magnets up to 7 Tesla are available and used in some research facilities (230).

An important factor in quantitative assessment of bone in MRI is accurate segmentation of bone and adjacent fat components such as marrow. Partial volume effects occur in these transition zones that may result in inaccurate differentiation of tissue type at these interfaces (236).

1.7 AIMS OF THESIS

In summary, the short and long-term consequences of disuse osteopenia, following lower limb fracture or surgery, may be profound in terms of predisposing patients to both immediate and future increased fracture risk. This potentially involves re-fracture at the original site or secondary fractures at other sites affected by bone loss, including the hip. Hip fractures are associated with high rates of morbidity and mortality with consequent social and economic impact. In 2000 there were approximately nine million osteoporotic fractures worldwide and 20% of these were hip fractures (21). As life expectancy increases globally, the number of hip fractures is likely to increase commensurately. Disuse effects in postmenopausal populations may be of significant importance as these women are already losing bone systemically due to decreased

oestrogen levels and are at greater risk of not recovering bone lost due to immobilization. Osteoarthritis is also a common condition in the postmenopausal age group that frequently necessitates joint replacement. A significant increase in hip fracture incidence in the year following TKR has been demonstrated (210) but the extent of disuse-related bone loss at the hip following TKR and its potential contribution to post-surgical fracture risk has not been reported. Earlier research on long-term unilateral disuse osteopenia is limited and most research on disuse-induced bone loss is focused on SCI, stroke patients, astronauts and bed-rest volunteers which may not be directly comparable to the effects of immobilization of a single limb. Further knowledge in this field, specifically in a postmenopausal population, may improve prediction of fracture risk and inform the use of pharmacological & mechanical interventions to mitigate bone loss in this group.

This longitudinal study will investigate the causes and effects of disuse osteopenia in four groups of postmenopausal participants: patients having sustained a recent leg fracture (< 3 weeks previously), leg fracture > 1 year ago, TKR surgery and controls. Baseline differences between the groups and long-term changes in physiological & functional parameters during recovery will be measured at intervals over a one year period. The following factors will be assessed:

1. DXA measurements of BMD at both hips and the lumbar spine.
2. DXA total body measurements of leg lean tissue mass (LLTM).
3. DXA AHA measurements of macro-architectural hip parameters.
4. DXA derived TBS measurements of trabecular micro-structure at the lumbar spine.

5. Changes in relative Left/Right Weight-Bearing (L/R WB) through the legs over time and during recovery.
6. Medical history of co-morbitities, medications and lifestyle factors, contributory to bone health, assessed by questionnaire.
7. Levels of pain, physical function and activity assessed by questionnaires and pedometer readings.
8. Levels of depression and anxiety assessed by questionnaires.

In addition:

The precision of a dual-scales method for measurement of L/R WB will be evaluated.

The utility of 1.5 Tesla MRI scanning, for the measurement of cortical bone and muscle mass changes at the proximal femur, will be investigated in sub-groups of control participants and newly fractured patients treated by plaster of Paris.

CHAPTER 2. MATERIALS AND METHODOLGY

This chapter describes the methods and materials used in the study. The safety and ethical concerns, and recruitment difficulties associated with the study design are also addressed.

The study utilised a prospective observational case-control study design to investigate the short- and long-term effects of disuse osteopenia at the hip resulting from immobilisation following lower limb fracture or total knee replacement (TKR) in a postmenopausal population. The long-term objective was to identify risk factors, resulting from immobilisation that may increase the likelihood of future fractures at the hip. The study focused on effects at the hip as fractures at this site have the most significant consequences for patients in terms of loss of function and mortality. Results from the study may help to identify when and to whom preventative treatments should be administered to reduce any bone density loss. The effects of immobilisation on functionality, quality of life and mental health (with regard to depression and anxiety), were also investigated. Changes in cortical bone and muscle mass at the proximal femur were investigated in sub-groups using 1.5 Tesla MRI scanning.

2.1 PARTICIPANTS

The study focused on postmenopausal women over the age of 45 years. This group was selected because they lose bone systemically (at a particularly accelerated rate in the two years post menopause) and may be potentially at greatest risk of not recovering bone lost following a period of immobilisation. Osteoarthritis is also a common condition in this age group, frequently requiring TKR as the end stage treatment for

severe disease. Although ankle fractures are not considered to be a typical osteoporotic fracture, this age group also frequently present with ankle fractures that often result from relatively minor trauma. An age-matched control population, with no history of lower limb fracture after the age of 21 years, was also recruited as a comparison for the other groups. Sub groups were selected for MRI scanning of the hip ROI to ascertain whether this methodology is suitable to measure changes in cortical bone geometry and muscle mass.

2.1.1 PARTICIPANT GROUPS

A sample size calculation was based on BMD loss at the ipsilateral femoral neck in a study by van der Poest Clement (12) in which significant loss (p=<0.01) of 5.1% was reported after an interval of one year following lower leg fracture in eleven participants. Baseline ipsilateral NOF BMD (0.78±0.15 g/cm^2) was low compared to that expected in the current study. Assuming a smaller loss of 2.0% BMD and based on a mean hip BMD of 0.812 g/cm^2 and a population standard deviation of 0.1 g/cm^2, a sample size of 25 participants per group was calculated(237) using an α value of 0.05 and β of 80%.

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Given the long-term commitment to the study required from participants, and the possibility of ill health or other difficulties arising in this age group, a high attrition rate (50%) was factored in to the study design (238). Fifty participants per group were therefore targeted for recruitment comprising the following:

50 x Control participants

50 x Patients undergoing total knee replacement

50 x Lower limb fracture patients treated by plaster of Paris (POP)

50 x Lower limb fracture patients treated by internal fixation (IF)

Sub-groups of ten volunteers were selected from each of the control and fracture populations to have MRI scans of their hips. The participants were ~~randomly~~ selected on the basis of their willingness to have the scans, absence of contra-indications for MRI scanning, and scanner availability at the time of their first appointment. Participants, who had TKR surgery or internal fixation of their fracture, were excluded from this element of the study as the implantation of metal fixation or prostheses is a contra-indication for the MRI scans.

2.1.2 INCLUSION CRITERIA

Fracture Cases

- Postmenopausal women > 45 years
- Fractured lower limb within past 2 weeks
- Immobilization > 6 weeks

TKR cases

- Postmenopausal women > 45 years
- TKR booked

Controls

- Postmenopausal women> 45 years

The fracture participants were recruited on the basis that their injuries were sufficiently severe to necessitate a minimum of 6 weeks without weight-bearing on the affected limb. Foot fractures were therefore excluded from this study, since they rarely require 6 weeks of immobilisation.

2.1.3 EXCLUSION CRITERIA

Cases

- Premenopausal women < 45 years
- Treatment of fracture by external fixation

Controls

- Premenopausal women < 45 years
- Corticosteroid use >2.5mg for >3 months within last 5 years.
- Lower limb fracture or TKR post age 21 years.
- Immobilisation of a lower limb for > 4 weeks within last 10 years or in postmenopausal period.
- Known knee osteoarthritis likely to result in a TKR within 1 year.

The exclusions were made on the basis of avoidable confounding factors known to have major effects on bone remodelling and quality (e.g. long-term corticosteroid use), or that may prohibit completion of the study (i.e. further leg surgery during the course of the study). Participants already on treatment for low BMD were not excluded as it was statistically probable that a high proportion of the study population would be in the osteopenic or osteoporotic range at baseline and already receiving treatment. It was expected that some participants would be diagnosed with low BMD during the course of the study and would commence treatment within the study period. It was felt important to keep the patients in the study as close to those seen in clinical practice as possible to ensure that the results are generalisable to the clinical population. Having a long list of exclusion criteria would mean that the population was screened to such an extent to not reflect the usual clinical population, which would also reduce the number of patients available for recruitment.

Previous immobilization could have residual effects on BMD in the affected limb and it was intended that cases with previous knee or total hip replacement (THR) would be excluded from all groups. In addition, the presence of a hip prosthesis would prevent DXA measurement at that site. However, it became apparent early in the recruitment process that enforcement of these exclusion criteria in the TKR group would severely limit the number of suitable respondents as bilateral OA in hip and knee joints (with consequent THR or TKR) was a common complication in these participants. Of the twenty-one TKR participants who completed the entire study, 5 had a previous TKR, 2 had a previous contralateral total hip replacement (THR) and 1 had both previous contralateral THR and TKR. Participants (particularly those with existing OA) frequently exhibited exacerbated pain in the contralateral knee or hip following surgery that unpredictably increased the probability of further surgery during the study period. One participant required a second TKR during the study period and was lost to follow-up for this reason. A further participant required a second THR after her third visit and her subsequent bone density data were unavailable.

2.1.4 RECRUITMENT

Patients were recruited immediately following treatment for traumatic fracture or before TKR surgery. Recruitment posters and leaflets (Appendix 1 & 2) were placed in the Emergency Department (ED) and fracture clinic at the Princess Elizabeth Orthopaedic Centre (PEOC) at the Royal Devon &Exeter (RD&E) Hospital to provide preliminary information about the project. Participants were also approached in the following ways:

- Suitable fracture patients were initially approached during their first appointment at the fracture clinic by staff involved with their treatment. They were given a patient

information sheet (PIS), (Appendix 3) and asked to contact the researcher if they were interested to participate.

- TKR patients were either approached by the clinical team during their clinic appointment or identified from the hospital waiting list and invited to participate by written communication (Appendix 4) that included the PIS and the researcher's contact details.

Controls were also recruited by a poster and leaflet campaign (Appendix 5 & 6). These were distributed around Exeter University campuses and other public places, such as gyms and health clubs, targeting people who might be interested to know about their bone health. Talks were given to selected groups with an interest in osteoporosis and leaflets distributed to anyone wishing to participate in the study. Prospective volunteers were asked to phone or write direct to the researcher to establish that they met the criteria to participate.

2.1.5 RESPONSE RATES

The control group was recruited easily and steadily as most participants recognized the benefit to themselves of discovering their BMD status. Once the initial volunteers were recruited, word-of-mouth communication amongst their peers proved a very effective recruitment method.

Recruitment of the TKR group was initially slow and recruitment via clinic staff was erratic. The strategy of direct mailing proved effective. All suitable participants, identified from the hospital surgery waiting list, were contacted and the group was recruited steadily.

The initial strategy for recruiting fracture patients via staff contact in fracture clinic was not successful for a number of reasons; in part due to lower than anticipated numbers of suitable fracture patients attending the RD&E Hospital. The study design required patients to attend the first data collection session within two weeks of sustaining their injury in order to obtain baseline data as close to injury as possible. This was not practical for many patients who were dependent on friends or relatives to provide transport following their injury. Patients frequently did not attend fracture clinic until many days after injury, having had initial treatment/casting in ED. Many patients attending fracture clinic were therefore effectively 'timed out' and eliminated as potential recruits. An attempt was made to approach patients in ED at the time of their first presentation with the injury, with caution in regard to any distress or confusion that patients were suffering at this time.

Although a number of named staff, both in fracture clinic and ED, were requested to focus efforts on recruitment for the project, difficulties were encountered in engaging other team members in this task due to the heavy workload, large numbers and high turnover of staff working in these departments. Attempts were made for the researcher to attend both fracture clinic and ED to approach patients directly. Although this was often successful, the infrequency and unpredictability of suitable patients being present at any given time, made this a prohibitively time consuming method of recruitment.

In order to complete the study within the given timeframe, some amendments to the original study design were implemented. Firstly, the two fracture patient groups, POP and IF, were merged reducing recruitment from a total of 100 patients to 50 patients. Secondly, for the convenience of patients and to facilitate recruitment of this group, the period of 2 weeks between injury and baseline measurement was extended to 3 weeks.

To address the issues of low recruitment in the fracture group, a cross-sectional arm was added to the study design. 50 additional volunteers were targeted who had sustained a leg fracture (resulting in approximately 6 weeks of immobilisation) more than one year previously, post menopause and within the previous ten years. This enabled comparison of bone changes due to previous immobilization against the control group. This 'cross-sectional' (Xsect) group were only required to provide baseline data and therefore only attended for one visit and one set of scans. These participants were recruited by the same methods used for the other groups i.e. direct approaches to members of the public by poster and leaflet campaign (Appendix 7 & 8) or written communication (Appendix 5) direct to patients who had previously attended at the RD&E Hospital as identified by the clinical teams. 2 participants in this Xsect group had sustained injury to the 5^{th} metatarsal of the foot but were included in the study as their fractures were of sufficient severity to require 6 weeks of immobilization.

The final groups recruited to the study were:

Group 1. Controls

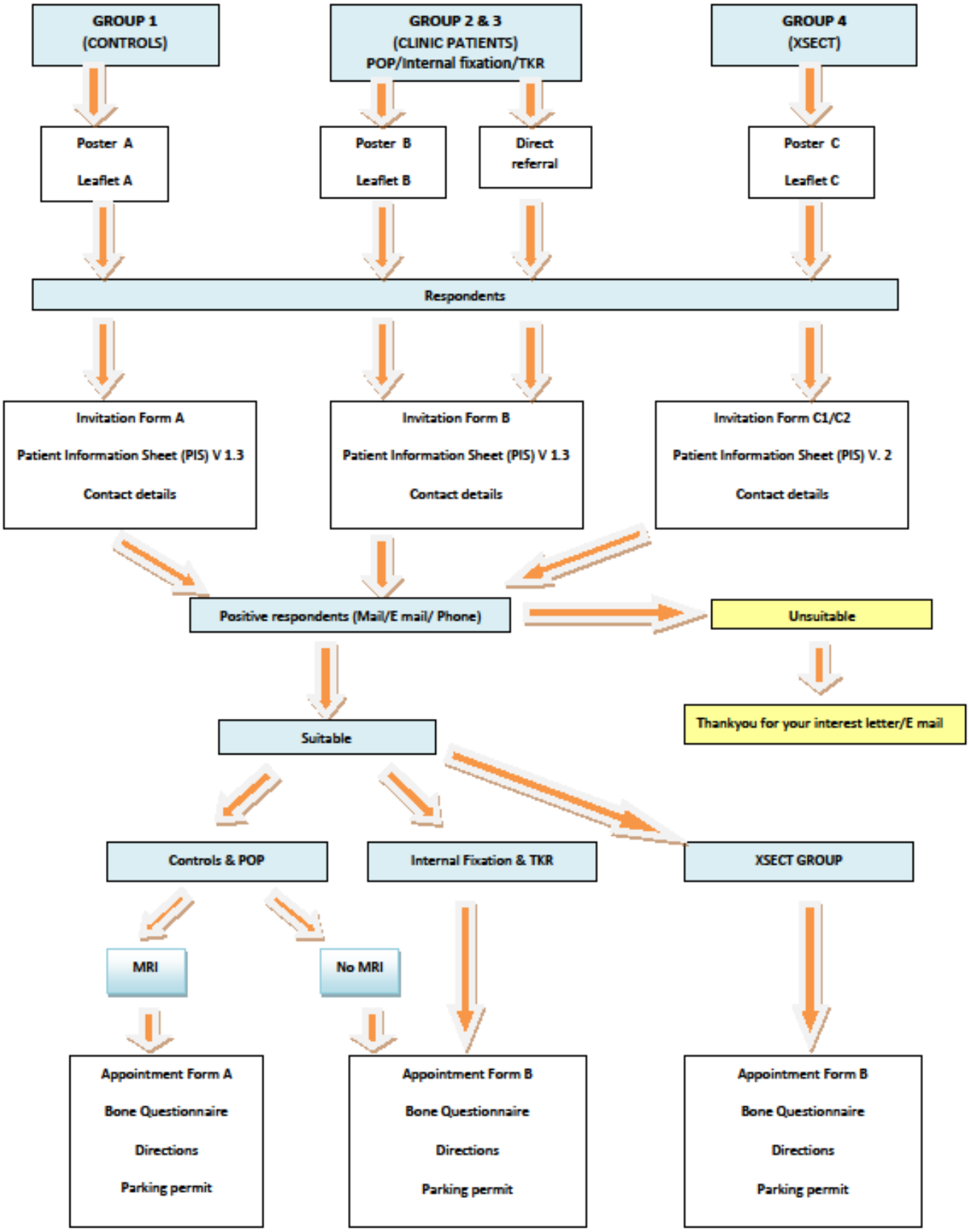
Group 2. TKR

Group 3. Fracture < 3 weeks before baseline data collection (#<3 wks)

Group 4. Fracture >1 year and <10 years before baseline data collection (#>1 yr)

The recruitment strategy is summarized in Figure 2.1

Fig 2.1. Recruitment strategy



The response rate for the various recruitment methods is summarised in Table 2.1.

Table 2.1. Participant recruitment summary

	Group 1 Controls	Group 2 TKR	Group 3 #< 3 wks	Group 4 #> 1 yr
Poster/Leaflet/Word-of-mouth				
Contacted	Unknown	Unknown	Unknown	Unknown
Volunteered	49	1	3	3
Suitable	46	1	1	3
Direct mailing				
Contacted	0	100	0	41
Volunteered	0	30	0	23
Suitable	0	30	0	23
Staff/researcher contact in clinic				
Contacted	0	0	Unknown	0
Volunteered	0	0	11	0
Suitable	0	0	9	0

2.1.6 RETENTION RATES

Table 2.2 shows the retention rates for the main study.

Table 2.2. Participant retention summary - Main study

	Recruited	**Data collection completed**			
		Visit 1	Visit 2	Visit 3	Visit 4
	n=	n=	n=	n=	n=
Controls	46	46	-	45	43
TKR	31	28	25	22	20
#< 3wks	10	9	9	9	9
#> 1yr	26	25	-	-	-
Total	113	108	-	-	-

Although the target of 50 participants was difficult to achieve for the patient groups, within the available time frame, retention rates for the study were much higher than

expected. Participants demonstrated a high level of interest and engagement with the project and attrition was mainly due to illness. This was particularly notable in the TKR group who had a higher co-morbity rate than the other groups. Three participants recruited to the study did not complete data collection at Visit 1. This was due to delayed or cancelled surgery. One participant completed questionnaires but was unable to have scans due to immobility that prohibited safe manual handling to position them on the DXA scanner. One TKR participant sustained a peri-prosthetic fracture following surgery and a further TKR participant required a second knee replacement during the course of the study. The attrition for all groups was minimal for the remainder of the project.

Table 2.3 shows the retention rates for the MRI study.

Table 2.3. Participant retention summary - MRI study

	Recruited	**Data collection completed**			
		Visit 1	Visit 2	Visit 3	Visit 4
	n=	n=	n=	n=	n=
Controls	11	9	-	9	6
TKR	0	-	-	-	-
#< 3wks	2	2	2	2	1
#> 1yr	0	-	-	-	-
Total	13	11	2	11	7

Two control participants were lost to the MRI element of the study because they were unable to enter the scanner due to claustrophobia. Four scanning sessions could not be completed at Visit 4 due to postponement of appointments by participants and unavailability of the MRI scanner at the rescheduled dates.

A grant application was submitted to the Society and College of Radiographers Industry Partnership Scheme (CORIPS). This was funded and provided travel and consumables

costs for the study in addition to conference attendance. The project was reviewed and approved by the Devon and Torbay Research Ethics Committee REC Ref: 09/H0202/64.

2.2 METHOD

2.2.1 PRELIMINARY ADMINISTRATION

- Positive respondents to the recruitment campaign were sent a PIS if they had not already received one and their contact details were recorded.
- Participants were recruited to the study if they met the inclusion criteria and did not have contra-indications for DXA scanning i.e. to minimise radiation exposure, participants were excluded if they had had a DXA scan within 6 months prior to the first appointment due on the study.
- Participants were asked if they were willing to have MRI scans and the MRI contraindication checklist (Appendix 9) was used to screen participants' suitability for this section of the study.
- Appointments were sent to suitable recruits using the appropriate forms that included relevant information on appropriate attire (with no metal fixings) for the scanning procedures. Travel information and a parking permit were provided. Where necessary, due to mobility problems, special arrangements were made to reserve a parking space close to the scanner facilities and to escort the participant using a wheelchair.
- To reduce the session time at Visit 1, a Bone Questionnaire (Appendix 10) was sent to participants to complete at their own convenience.

2.2.2 DATA COLLECTION SCHEDULE

Data collection was conducted at the Children's Health and Exercise Research Centre (CHERC) and the Peninsula MR Research Centre (PMRRC) at St.Luke's Campus of the University of Exeter.

Participants attended data collection sessions at the intervals shown in Table 2.4.

Table 2.4. Schedule of visits for different groups

	2 weeks pre-baseline	Baseline*	6 weeks post baseline	6 months post baseline	12 months post baseline
Controls					
TKR					
#< 3wks					
#> 1yr					

* Baseline = Surgery date for TKR or within 3 weeks of fracture (at participant's convenience for control and #> 1 yr groups).

Some difficulties arose in obtaining baseline data within a 2 week period prior to surgery for the TKR group as a number of participants had unexpected postponements to their surgery following Visit 1. The mean interval between Visit 1 and surgery was 22.5 days for the TKR group. The mean interval between injury and Visit 1 for the #< 3 week group was 19.7 days.

2.2.3. SCREENING AND DATA COLLECTION PROCEDURES AT VISIT 1

Preliminary consenting and checks

- Informed consent was obtained having ensured that participants had read and fully understood the information provided to them.
- Before DXA or MRI scans took place, participants were asked to confirm that they were post menopause and therefore could not be pregnant.

- The Bone Questionnaire provides participants' GP contact details plus their medical and lifestyle history relating to bone health. This questionnaire was checked in the participant's presence enabling them to clarify or complete any missing information.

Questionnaires

Permissions were obtained to use copyrighted questionnaires in the study. Validated questionnaires were selected on the basis of their reliability, precision and relevance to the age range and pathologies of the study population. To achieve comparability and continuity in participant responses, questionnaires were administered during the data collection sessions by the same researcher at each visit. As some of the questions were sensitive and possibly intrusive in nature, participants were offered the opportunity to complete the questionnaires at home if they preferred, however no participants opted to do this. As questions were posed to all groups irrespective of the presence of lower-limb problems, answers regarding depression, anxiety, pain, perception of health state and quality of life were not restricted to direct association with leg injury/surgery.

- A visual pain scale was used with score range from 0 (no pain) to 100 (intolerable pain). In order to assess the overall impact of pain on function and wellbeing, participants were asked to give a generlised assessment of their pain levels i.e. not relating only to their fracture injury or TKR surgery. This was because these participants frequently exhibited referred pain in their hips or contralateral limb during recovery. Some participants also suffered shoulder pain as a result of using crutches.
- The Lower Extremity Functional Scale (LEFS) (Appendix 11) developed by Binkley et al (239) was used to assess functional ability and recovery. This questionnaire has 20 activity domains each with 5 levels of difficulty. A maximum

score of 80 represents full functionality in all domains. The LEFS questionnaire relates to lower limb functional impairment only, however many of the patient participants experienced secondary problems in their overall function due to shoulder pain resulting from use of crutches, or to referred pain in the spine or contralateral limb associated with alterations in their gait and distribution of weight-bearing. Questions regarding lower-limb functional impairment are not directly applicable to the control group (although they may experience functional limitations due to other factors), therefore, in order to achieve comparability between the different groups, all participants were asked to answer questions relating to functional difficulties due to any physical reason regardless of the association with lower-limb injury or surgery.

- A quality of life questionnaire (EQ5D)* (Appendix 12) was administered to provide a basic assessment of difficulties with mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Scores range from 5 (best possible) to 15 (worst possible). A visual scale ranging from 0 (worst imaginable) to 100 (best imaginable) provides a score of the participant's state of health as they perceive it to be.
- The Patient Health Questionnaire (PHQ-9)** (Appendix 13) was used to assess the psychological impact of injury/surgery and immobilisation. With 9 domains and 4 levels, scores range from 0 (best possible) to 27 (worst possible).
- Additionally the Generalised Anxiety Disorder questionnaire (GAD-7)*** (Appendix 14) was used for the same purpose. With 7 domains and 4 levels, scores range from 0 (best possible) to 21 (worst possible).
- Participants were asked to take home and complete the International Physical Activity Questionnaire (IPAQ) (Appendix 15).This questionnaire contains questions

about the types, intensity and duration of activity for a 7 day period immediately following their visit. There was high degree of subjectivity in the questions asked in this questionnaire as participants varied in their concept of vigorous and moderate activity, largely according to their own current level fitness and mobility. Although the form provides some guidance as to which activities are moderate or vigorous, in an attempt to achieve some level of consistency, all participants were asked to consider general housework as moderate activity and heavier housework (such as cleaning windows or changing duvet covers) as vigorous. It should be noted that the IPAQ was developed and tested for use in an age range of 15 to 69 years. Whilst some participants in this study were above this 69 year limit, this was the most appropriate validated questionnaire available for the majority of participants and as many of the older participants in the study demographic were very active, the questions were considered appropriate.

Measurements

- Height was measured to the nearest 0.01m using a wall mounted stadiometer (Seca, Germany).
- Total weight was measured to the nearest 0.1 kg using weighing scales (Seca 877, Germany).

**©1990 EuroQol Group. EQ-5D ™ is a trade of the EuroQol Groupmark (Appendix 12).*

*** Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. Copyright © 2005 Pfizer, Inc. All rights reserved. Reproduced with permission (Appendix 13).*

****GAD-7 Copyright Pfizer Inc. all rights reserved; used with permission (Appendix 14).*

- Left/right weight-bearing was measured using two sets of identically calibrated weighing scales (Seca 877, Germany). Ensuring stability of the scales, participants were positioned in a natural standing posture astride two sets of scales. Three random consecutive readings, recorded from the left hand side, were taken with the researcher standing slightly behind the participant to minimise any influence on their balance. The average of these three readings was calculated as representative of the participant's left side weight-bearing. The right measurement was calculated as the difference between left average weight-bearing and the participant's total weight. A precision study (240) was undertaken to validate this technique and is described in Chapter 3.
- All participants underwent DXA (GE Lunar Prodigy, Bedford, MA) scans of bilateral hips, lumbar spine and total body in accordance with the manufacturer's protocols. The lumbar spine and hip scans are clinically relevant sites for scanning and enabled the diagnosis of low bone density or osteoporosis. The total body scan provided measurements of body composition in addition to total bone density. The bone mineral density, fat and lean mass can be divided into subsections, providing regional measurements of changes in bone density and lean tissue mass in the lower limbs.

The total radiation effective dose equivalent for the entire study was estimated at 7.8 µSv for the average control participants and 10.4 µSv for the average case. The risk benefit assessment (Appendix 16) shows that this represents a trivial risk compared to the daily background radiation (depending on location).of 6 to 20 µSv. Allowing

for a repeat exposure due to positioning inaccuracy or equipment failure, a dose constraint of 15 µSv was set for each participant in the study.

Correct patient positioning was important to obtain accurate reproducible measurements and standard protocols were followed by a single researcher to avoid inter-operator variation. Training was undertaken by the operator at the RD&E DXA department to learn the correct positioning techniques. Where necessary, due to plaster casting or discomfort following surgery, standard positioning was adapted with supports. These adaptations were reproduced at all scanning intervals to achieve directly comparable results between scans.

Quality Assurance (QA) tests, assessing functional performance and calibration, were performed on the DXA scanner using a QA phantom to ensure safe and accurate operation before the start of each day's scanning session. In addition regular QA tests were performed using a manufacturer-supplied aluminium spine phantom (number 15867). The QA precision results for the equipment over the period of the study are shown in Figures 2.2 and 2.3.

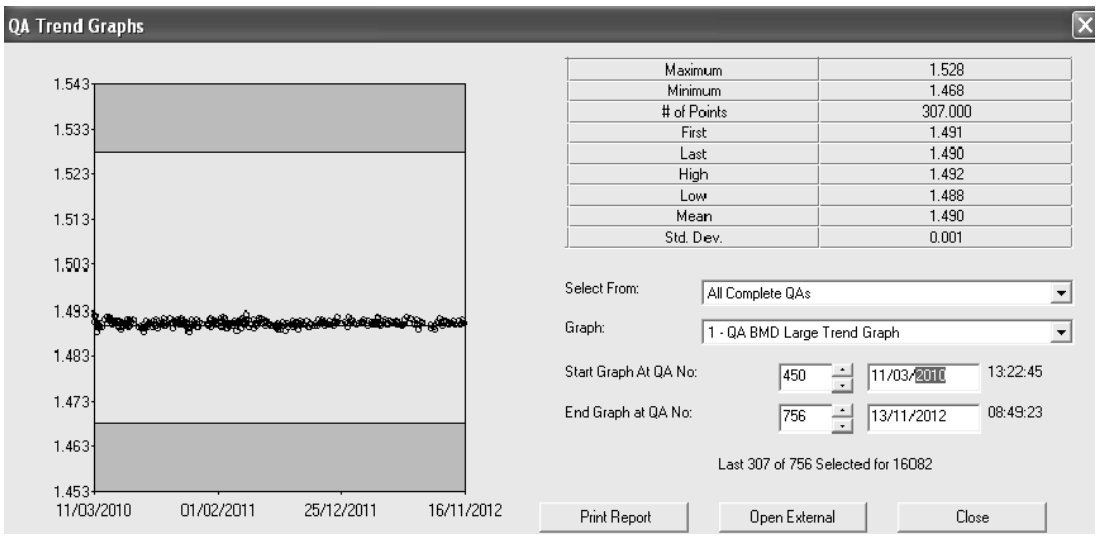
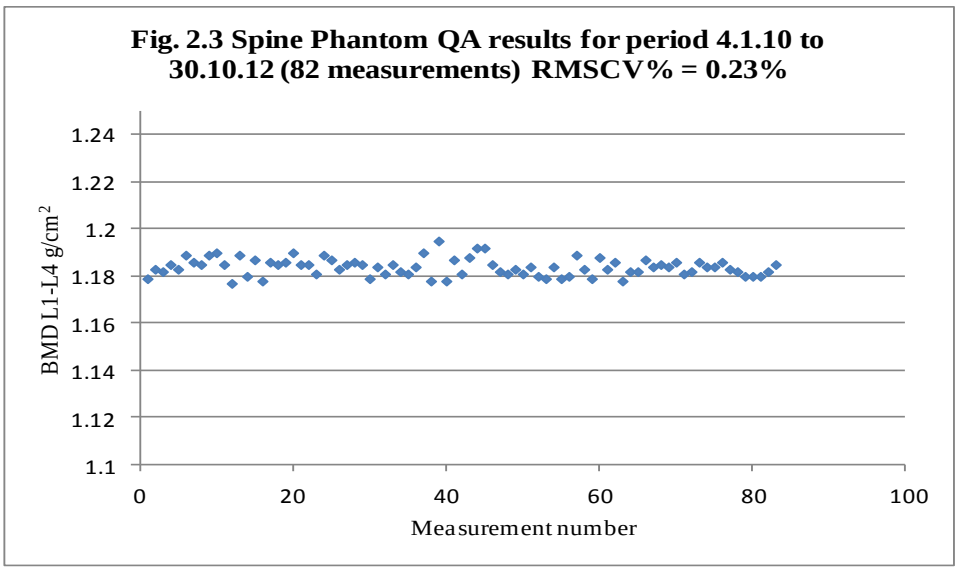


Fig 2.2 BMD QA results over the total study period.



The precision error of DXA scanners is typically quoted as being in the region of 1%, however a recent study (224), on the scanner used in this study, demonstrated higher precision errors in overweight and obese groups. The Knapp et al study performed lumbar spine, left hip and total body scans on female participants and repeated these after a short interval during which participants were removed from the scanner and walked around the room. The effect of BMI on precision error at the hip ROI was limited, meaning that this is a good site for measuring changes in BMD even in obese participants. Data for 91 participants (mean age 47±13 yrs) available from the Knapp et al. study were used to assess short term precision error (STPE), calculated using the root mean squared coefficient of variation (RMSCV%), for the range of parameters shown in table 2.5. The table summarises the STPE results for all 91 participants without subdivision into BMI groups.

Table 2.5. Short term precision error in DXA measurements.

Measurement	RMSCV%
BMD spine L1-L4	1.29
BMD at Total Hip	0.92
BMD at NOF	1.58
Fat-Total body	2.19
Lean tissue-Total body	1.57
TBS	2.07
AHA - Hip Axis Length (HAL)	0.66
AHA - Cross Sectional Moment of Inertia (CSMI)	3.94
AHA – Cross Sectional Area (CSA)	2.90
AHA – Femur Strength Index (FSI)	9.80

- Subgroups selected for MRI were scanned at the hip region at each of their visits over the one year period using a 1.5 Tesla Philips Intera scanner. Participants were scanned in a supine position using a SENSE 4 element body coil. The same operator positioned participants and performed the scans for all examinations. Data were acquired for coronal and axial sections using the sequences and scanning parameters shown in Table 2.6. The T1 weighted turbo spin echo sequence was selected as this provides good contrast between bone and soft tissue. The STIR TSE and PDW SPAIR sequences were included as a secondary option. Whilst these sequences do not give the same level of tissue contrast as T1W TSE and are therefore less easy to interpret, they are not susceptible to chemical shift image artefacts that can occur at tissue interfaces and cause potential measurement error (241).

Table 2.6. MRI scanning protocol

Plane	Sequence	Acquisition voxel size (mm)	Reconstruction voxel size (mm)	Minimum slice gap (mm)
Coronal	T1W TSE*	1.97/2.11/5/00	0.99/0.99/5.00	5
Coronal	STIR TSE†	1.97/2.11/5/00	0.99/0.99/5.00	5
Axial	T1W TSE*	1.97/2.11/5/00	0.99/0.99/5.00	5
Axial	PDW SPAIR‡	1.97/2.11/5/00	0.99/0.99/5.00	5

** T1 weighted Turbo spin echo*

†Short T1 Inversion Recovery Turbo spin echo

‡Proton Density Spectral attenuated Inversion Recovery

- Pedometer readings: Participants were asked to take home a pedometer and use it in accordance with the Activity Monitor Instructions provided to them (Appendix 17) for 3 days in the week following their visit. For comparability with the #>3 week group, TKR patients were asked to perform the pedometer measurements immediately following surgery.

2.2.4. SCREENING AND DATA COLLECTION PROCEDURES AT VISIT 2, 3 & 4

Questionnaires and measurement procedures, as described for Visit 1, were repeated at the follow-up visits. However, to avoid unnecessary radiation exposure, the Lumbar Spine scan was not performed at visit 2 because changes in this region were not expected within the 6 week immobilisation period. In order to achieve consistent patient positioning, allowing accurate comparison of repeat scans, previous scans were checked so that the original positioning could be reproduced. This was particularly necessary for

the patient groups where positioning at the first visit may have been affected by plaster casts or the use of supports.

The MRI screening questionnaire was used at every visit to ensure that no contraindications had arisen since the previous visit.

The following additional questionnaires were designed and used at the follow-up visits:

- Immobilization record (Appendix 18) in which periods of total and partial immobility were recorded.
- Treatment and falls record (Appendix 19) in which any further changes in fractures, drugs or diseases, and physical therapies known to affect bone metabolism were recorded.

2.2.5. COMPLETION ADMINISTRATION

- Participants were provided with their bone mineral density results during their visits, which may have indicated the presence of osteopenia or osteoporosis. They were advised that the researcher was a student and that this was not an official diagnosis. Their fracture history and other osteoporosis risk factors were assessed from the questionnaire and included in a report prepared by the researcher and approved by Dr. K. Knapp (project supervisor). With participants' consent, abnormal results were sent to their GPs.
- The consultant orthopaedic surgeon responsible for care of the TKR patients was informed if any of these participants exhibited BMD in the osteopenic or osteoporotic range.

- Some of the newly fractured patients may have been identified by the RD&E as requiring DXA scans as part of their clinical care. To avoid scanning duplication, a list of participants from this group was supplied to the relevant team at the RD&E hospital.
- Follow-up appointments were sent to participants and their travel expenses reimbursed.
- Newsletters were distributed at appropriate intervals to inform participants about progress with the project.
- Progress reports were prepared at designated intervals for the Research Ethics Committee (REC), NHS Research and Development Department and for the funders of the study, CORIPS.

2.2.6 SAFETY & ETHICAL CONSIDERATIONS

The following safety and ethical issues in the study design were addressed to minimise any potential adverse effects, pain, discomfort, distress, intrusion, or inconvenience to participants:

All participants were given a PIS with a copy of the consent form attached to enable them to thoroughly read and understand the contents before volunteering. An opportunity to ask further questions regarding the study was offered before signed consent was requested at the time of the first appointment. Participants from vulnerable groups were not approached. To avoid any possibility of patients sensing coercion by hospital staff or the researcher, patients (who were directly approached in ED and fracture clinic and who expressed willingness to participate) were asked to read the PIS

at home and contact the researcher later to make an appointment after they had fully considered all the information provided to them.

The main potential risk in this study arose from the ionising radiation used for the DXA scans. Despite the number of scans involved, the dose was very low, at a total of approximately 10 microSieverts over the entire study, roughly equivalent to the risk involved with 1 day's exposure to the sun without sunscreen. Participants were assured that this is a very small dose and whilst there are risks of stochastic/"chance effects" occurring, these are very small. DXA scans are usually stress-free, painless and comfortable. Participants were shown the equipment and had the procedure explained to them prior to the scan.

The MRI scan does not use ionising radiation although heating effects have been noted with MRI. The protocols used for MRI ensure that any heating effects are kept to a minimum and that the heating falls within the safety limit of an increase no greater than 1% to the total body temperature during the scan. All participants undergoing MRI underwent strict safety screening and completed the MRI contraindications checklist to ensure that they were suitable to enter the magnet. The MRI scanner may be claustrophobic for some participants. Where this was the case, participants were not encouraged to proceed and were able to opt out of this part of the study. MRI scanning is a noisy procedure and all participants were provided with headphones and music if desired.

To minimise the time burden for participants, questionnaires were selected for their brevity and ease of completion. It was possible that questions regarding the depression and anxiety status of participants could have been sensitive and upsetting for them,

although the questions were not highly specific in nature. A mood disorders protocol was in place for risk assessment and reporting should any participant be identified from their responses as being at a significant risk of harm (Appendix 20). Training in the use of this protocol was undertaken at the University of Exeter's Mood Disorders Centre before the study commenced. Participants were offered the option to complete the questionnaires at home and return them by post if they preferred.

The total visit time averaged approximately 1 hour for most participants and about 2 hours for those having MRI scans. Arrangements were made to reserve a parking space and provide a wheelchair escort for any participant who was experiencing difficulty in walking after injury or surgery. No incentives or payments were made to participants but parking permits were provided and travel expenses reimbursed.

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Data collection and DXA scanning was undertaken by a single researcher working alone. It was therefore important to be mindful of potential safety issues for both participants and researcher in this context. Where there were any concerns about transporting participants or manual handling, due to immobility, the scanning procedures did not proceed. The University of Exeter indemnity arrangements applied to the study and personal indemnity cover for the researcher was provided through her membership of the Society of Radiographers.

Confidentiality issues were addressed by employing the following safeguards. Data files for analysis were de-identified and participants provided with a unique identifier code. Computerised DXA data files were identified by participants' initials and unique identifier. Only individuals authorised to use the DXA laboratory were permitted access

to the password protected computer. Computerised MRI data files were stored under a unique identifier and access to these limited to MR staff. Hard copies of data and material containing participant contact details were stored in a locked filing cabinet in a private office with access only available to authorised personnel.

2.3 DATA ANALYSIS & STATISTICS

The primary outcome measures for the study are:

- Changes in bone mineral density and lean tissue mass.
- Changes in bone quality and structural parameters measured by AHA and TBS

The secondary outcome measures are:

- Relationships between longitudinal changes in bone mineral density and fracture risk at the hip.
- Changes in mood as measured by anxiety and depression questionnaires.
- Changes in functionality and quality of life.
- Changes in cortical bone and muscle thickness as measured by MRI.

Statistically, it was probable that a high proportion of participants would be diagnosed with osteopenia or osteoporosis as a result of taking part on the study and would consequently be put onto treatment. Table 2.7 shows a summary of all participants (who were included in the final analysis) receiving treatment for low bone density at baseline, and additional participants put onto treatment during the course of the study. Data for two participants, who completed the study, were ultimately excluded from the final analysis of results because they were prescribed strontium ranelate which is a drug for the treatment of osteoporosis known to artificially elevate BMD measurements due to

its high atomic number, (Z=38) compared to calcium (Z=20), causing greater attenuation of X rays (242).

Table 2.7. Summary of participants receiving treatment for low bone density at baseline, and additional participants put onto treatment during the course of the study.

	Visit 1	Visit 2	Visit 3	Visit 4	Total
Calcium supplement	3	3	3	4	11
Bisphosphonate + Calcium	11	0	8	3	22

2.3.1 ANALYSIS OF DXA SCANS

Raw data from the DXA scans were analysed using the GE Lunar enCORE™ 2005 software version 9.30.044. This software automatically detects the bone edges of the ROI and subdivides that region as shown in Figures 2.4 and 2.5.

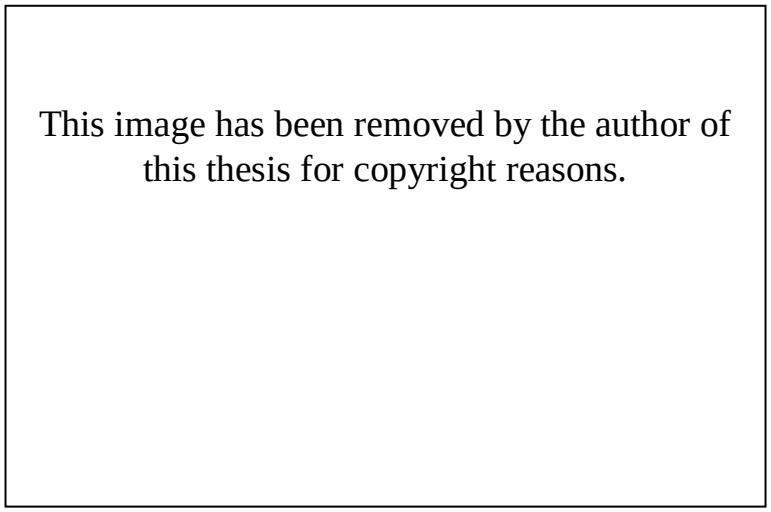


Fig 2.4 DXA image showing ROI subdivisions of the hip region (243)

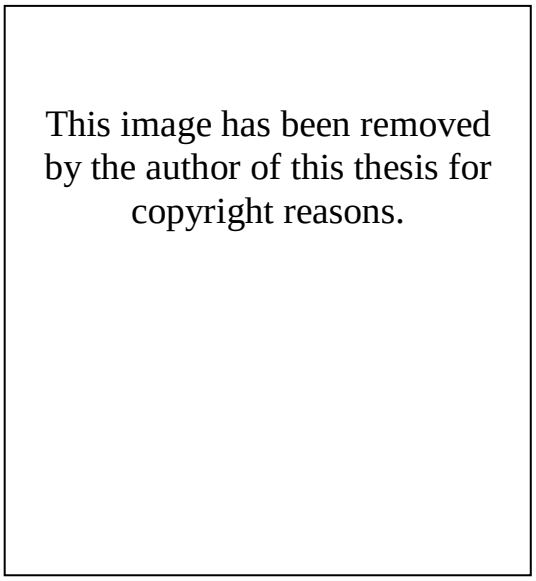


Fig 2.5 DXA image showing ROI subdivision of the spine into individual vertebrae (L= Lumbar, T=thoracic) (243)

The subdivisions demarcated in the total body scans are shown in figure 2.6.

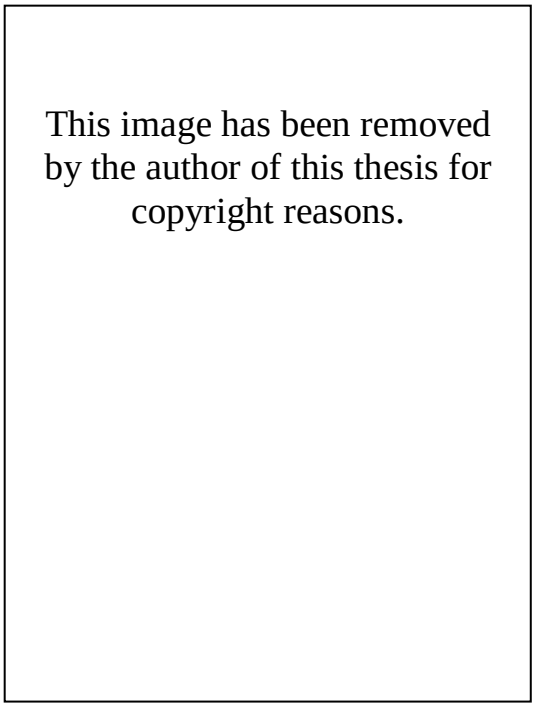


Fig 2.6 Total body scan regions of interest (244).

The regions demarcated by the computer were checked by the researcher for any anomalies and manual adjustments made where appropriate. For consistency in analysing the follow-up scans, the ROIs from the original scan were copied and transferred onto the new scan images. Where there were differences in the patient position between the original and follow-up scan, manual corrections were applied as appropriate. The scanner output provides bone densitometry and body composition results and calculates T & Z scores based on the National Health and Nutrition Examination Survey (NHANES) database. The enCORE™ 2005 software version 9.30.044 also automatically provides AHA results of hip geometry and strength. An example of the DXA output is shown in Appendix 21. A macro was used to transfer the DXA data to Microsoft Excel Spreadsheets.

TBS (TBS iNsight®, v1.8. Med-Imaps, France) software was used to analyse all lumbar spine scans. TBS uses the same raw data, edge detection and ROIs that generate the bone densitometry results and provides a visual representation of TBS values in the lumbar spine together with regional scores for bone microarchitecture. An example of the TBS report is shown in Appendix 22. TBS scores are based on data for French Caucasian women and range from 0.9 to 1.6 where a low score represents a poor/deteriorated bone microstructure with low connectivity, high inter-trabecular spacing and a low number of trabeculae. The TBS scoring system and relationship to bone quality is shown in Fig 2.7.

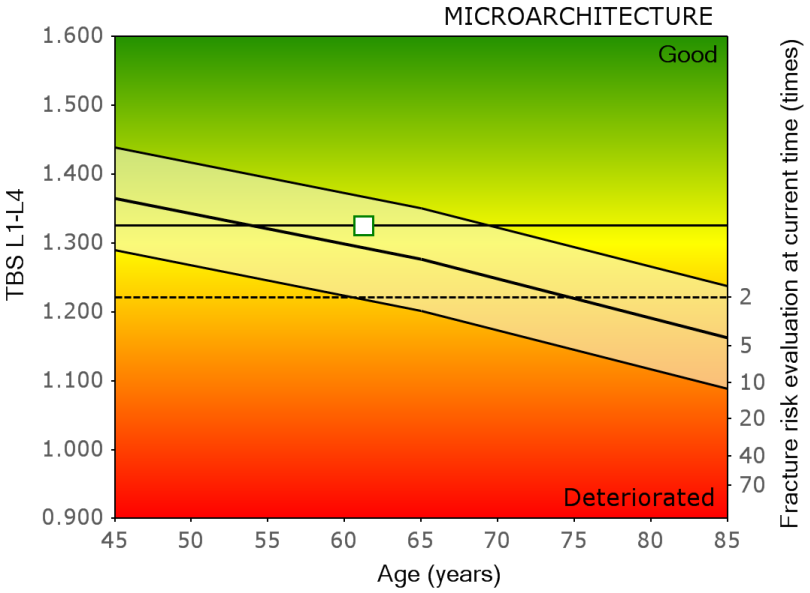


Fig 2.7. TBS scoring system and relationship to bone quality (245)

2.3.2 ANALYSIS OF MRI SCANS

Data from the coronal images only, for five control participants who provided useable images and completed the MRI scans at the end of the one year period, were analysed using OsiriX v.3.9.4 software. The number of fracture participants suitable for MRI scanning was insufficient to provide meaningful results and these were therefore excluded from the final analysis. Measurements were made from the anonymised images at the sites shown in Figure 2.8 and described in Table 2.8.

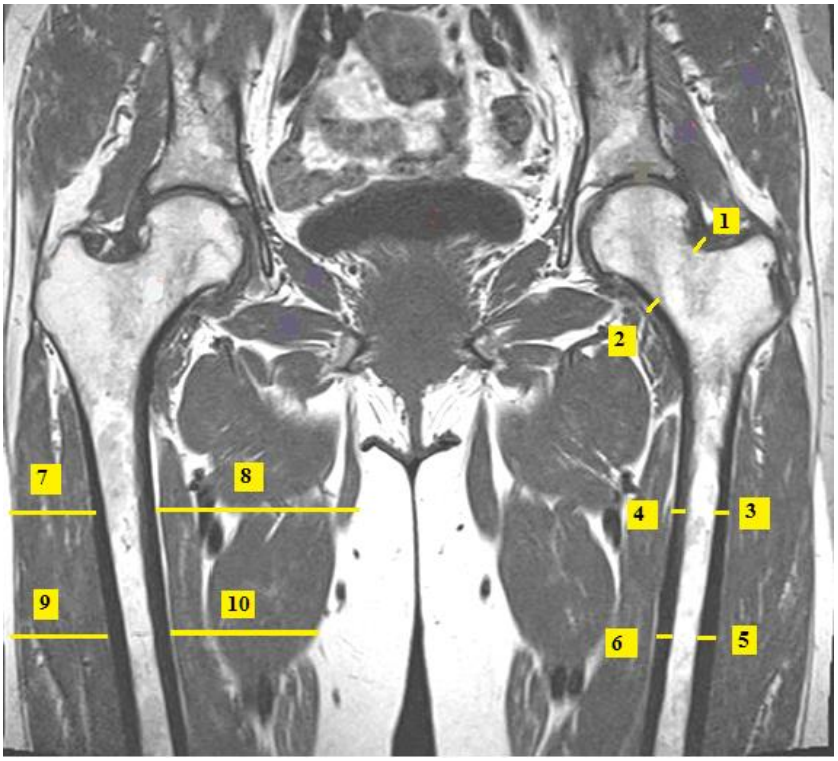


Fig. 2.8. Measurement sites of cortical bone and muscle tissue thickness. The numbered sites represent the measurement location; actual measurements were obtained perpendicular to the femoral neck or shaft.

Table 2.8. MRI measurement site descriptions

SITE	Tissue	Level		Position
1	Cortical	A	Lateral	Perpendicular to Mid femoral neck
2	Cortical	A	Medial	Perpendicular to Mid femoral neck
3	Cortical	B	Lateral	9 cm inferior to superior aspect of greater trochanter
4	Cortical	B	Medial	9 cm inferior to superior aspect of greater trochanter
5	Cortical	C	Lateral	14 cm inferior to superior aspect of greater trochanter
6	Cortical	C	Medial	14 cm inferior to superior aspect of greater trochanter
7	Vastus lateralis muscle	B	Lateral	9 cm inferior to superior aspect of greater trochanter
8	Medial muscle compartment	B	Medial	9 cm inferior to superior aspect of greater trochanter
9	Vastus lateralis muscle	C	Lateral	14 cm inferior to superior aspect of greater trochanter
10	Medial muscle compartment	C	Medial	14 cm inferior to superior aspect of greater trochanter

A single operator performed the image analysis and was instructed to take measurements of cortical bone and muscle compartments perpendicular to the femoral neck and femoral shaft at the levels indicated in Figure 2.9. The aim was to ascertain long-term change in bone and muscle measurements rather than to compare specific sites between individuals; therefore these levels were used consistently for all cases irrespective of the overall body height or femur length of the individual participant.

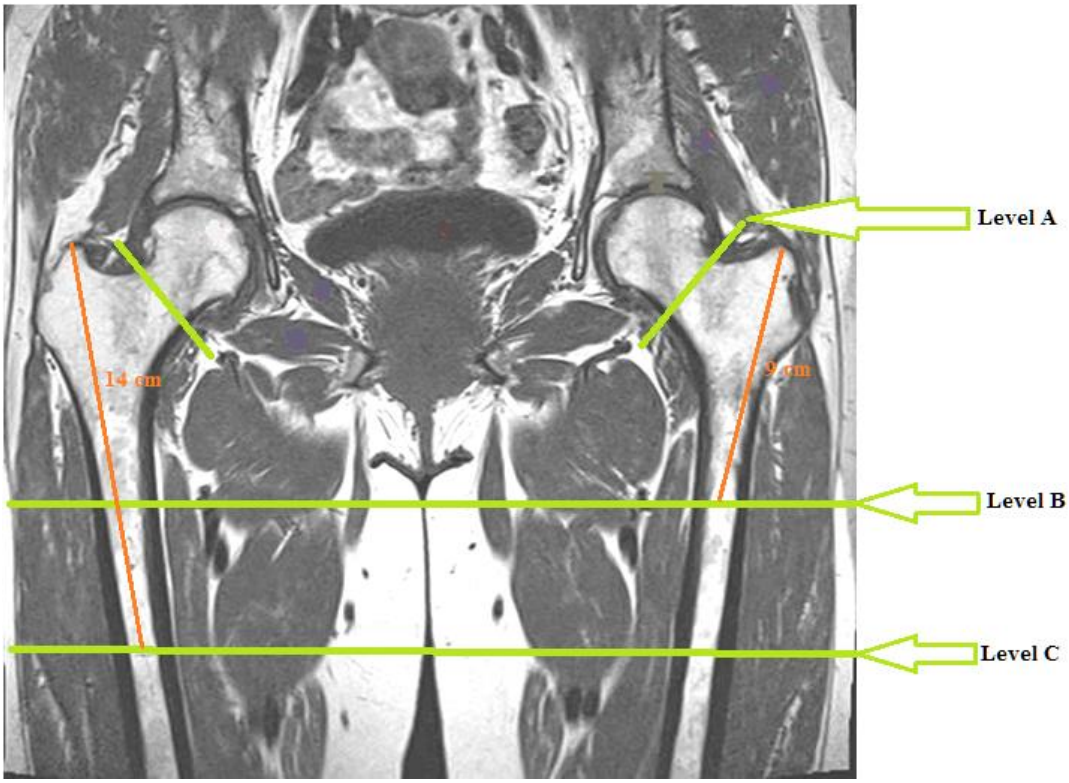


Fig. 2.9. Levels selected for measurement of cortical bone and muscle tissue thickness.

2.3.3 ANALYSIS OF QUESTIONNAIRES

Questionnaires were scored in accordance with the designers' instructions.

2.3.4 STATISTICAL METHODS

After making appropriate exclusions for confounding cases, data for 95 participants were ultimately analysed as shown in Table 2.9.

Table 2.9. Summary of participants included in final data analysis.

Group 1 Controls	Group 2 TKR	Group 3 #< 3 wks	Group 4 #> 1 yr
43	19	9	24

Data from questionnaires, weight, height and left/right weight-bearing measurements were de-identified and entered into Microsoft Excel spreadsheets. BMI was calculated as weight in kg/height m^2. No weighting was given for duration or level of treatments, medications or medical conditions and these were coded as dichotomous variables. Raw data from the DXA scanner were downloaded and converted to a macro for transfer to Microsoft Excel. Left and right side DXA measurements were re-designated as ipsilateral and contralateral sides. The left side was designated as the ipsilateral side for the control group.

Data were cleaned of errors and inconsistencies and analysed in PASW statistics version 18 (IBM Armonk, NY). Distributions for all parameters were tested for normality and parametric or non-parametric statistics used as appropriate. Descriptive statistics are reported as means and standard deviations, percentage of group, and as medians and interquartile ranges for Gaussian and non-Gaussian data respectively. Longitudinal changes in parameters are presented graphically (SigmaPlot v. 12). Significant differences between the groups are reported, calculated by Independent Samples t Test (2-tailed) for parametric variables and Independent Samples Median

(Fisher's Exact) Test for non-parametric variables. Significant differences in measurements, at intervals over the study period, compared to the baseline measurement are also reported, calculated from Paired Samples t Test for parametric variables and Related-Samples Friedman's Two-way Analysis of Variance by Ranks for non-parametric variables. The significance of differences between ipsilateral and contralateral measurements was calculated by Paired Samples t Test.

Stepwise multiple regression analyses (PASW statistics 18) were performed on a cases excluded listwise basis, and reported using unstandardised coefficients. Potential confounding factors, such as the presence of a previous TKR, treatment for osteoporosis, age and BMI, were included as explanatory variables in the models.

Specific statistical methods used for the sub-studies evaluating the dual scales and MRI techniques (chapters 3 and 4) are described in the relevant chapters.

CHAPTER 3. EVALUATION OF A DUAL-SCALES METHOD TO MEASURE WEIGHT-BEARING THROUGH THE LEGS, AND EFFECTS OF WEIGHT-BEARING INEQUALITIES ON HIP BONE MINERAL DENSITY AND LEG LEAN TISSUE MASS

3.1 INTRODUCTION

This chapter investigates the accuracy of measuring relative left/right weight-bearing (L/R WB) through the legs using two identically calibrated weighing scales. The short-term weight-bearing (WB) tendencies in a general population of nine participants (Group A) and the long-term WB tendencies in forty-two females from the control group of the main study (Group B) are assessed. The effect of weight-bearing inequalities at baseline on hip bone mineral density and Leg Lean Tissue Mass (LLTM) in Group B are also investigated.

This study required a convenient and reliable method to monitor changes in L/R WB during recovery following leg fracture or TKR. A number of studies investigating re-ambulatory function, activity and recovery following injury or surgery, use technologically sophisticated methods, including force plates and portable monitoring devices such as accelerometers, to assess changes in patients' weight-bearing activity and return to 'normal' gait (209, 246-249). These devices can provide comprehensive information for complex gait and activity analysis and although force plates were available at the research facility where the study was conducted, they were located remotely from the main data collection area and were not readily accessible to participants with limited mobility. The necessity for the researcher, working alone, to

transport some participants by wheelchair from one facility to another, prohibited the use of this equipment on the grounds of manual handling difficulties, safety and convenience for both participant and researcher. A simple, inexpensive and reliable alternative was required that could be used in the main research area to provide basic information on standing weight-bearing and balance. It is evident that a dual-scales method is currently used in some clinical situations to monitor L/R WB changes in patients recovering from conditions that are associated with postural imbalance. Although this is a simple option, no published studies have been found that have investigated the precision of this method either in the short or long-term. Prolonged immobilization, reduced weight bearing activity and altered L/R WB are inevitably associated with leg injury or surgery potentially resulting in either unilateral or bilateral loss in BMD and leg muscle mass (6-13). In order to investigate the effects of altered L/R weight distribution in an injured study population using the dual- scales method, it was first necessary to assess the accuracy of the method, and the normal L/R WB variation of a general population in the immediate short term. L/R WB in the uninjured control sample, from the main study on Disuse Osteopenia in a postmenopausal female population, was investigated to assess whether minor/normal inequalities in L/R WB at their baseline visit were associated with any differences in L/R BMD and LLTM. L/R WB measurements for this control group, taken at three six-monthly intervals, were used to assess the long-term variation in their L/R WB tendencies.

3.2 AIMS AND OBJECTIVES

This study investigated: 1. (a) The accuracy of a method for measuring L/R weight distribution using two sets of identically calibrated scales and (b) the short-term variation of L/R WB tendencies in a general population sample comprising a mixed age

and sex group of 9 volunteers (Group A). 2. (a) The effect of L/R WB inequalities at baseline on BMD at the hip and on LLTM measured by Dual Energy X-ray Absorptiometry (DXA) and (b) the long term L/R WB tendencies in the control group from the main study (Group B).

3.3 METHODS & STATISTICS

3.3.1 *Participants*

1. Group A comprised a mixed sex group of 9 volunteers (aged 19-54 years). Volunteers were recruited from students, staff and members of the public available at the Children's Health and Exercise Research Centre, University of Exeter. No exclusion criteria were applied other than absence of an adult history of leg fracture or surgery,

2. Group B consisted of 42 postmenopausal women > 45 years, with no history of leg or ankle fracture, from the control group of the main study.

Participant characteristics for Groups A&B are shown in Table 3.1.

Table 3.1. Participant Demographics

	Group A (*n*=4 m, 5 f) Mean (SD)	**Group B** (*n*=42 f) Mean (SD)
Age (years)	36.2 (17.0)	64.6 (7.6)
Height (m)	1.68 (0.08)	1.64 (0.05)
Weight (kg)	73.8 (8.2)	68.7 (10.0)
Body Mass Index ($kg.cm^2$)	26.1 (2.9)	25.5 (3.13)

SD: standard deviation

3.3.2 *Methods*

1. (a) Three participants from Group A were weighed on one set of scales to establish

their true total weight. The scales were calibrated equally by placing identical weights on each. Ensuring stability of the scales, participants were then positioned in a natural standing posture astride two sets of scales (Seca 877, Germany) as shown in Figure 3.1. Participants were instructed to stand in a forward facing position that they would naturally adopt when standing still with no specific instruction given regarding the placement of their feet on the scales. They were asked to look directly ahead, (to prevent participants adjusting their stance when seeing their readings), and were also asked not to speak during the measurement to avoid unnecessary movement. As it is not possible to simultaneously read both left and right digital readouts (due to the inherent tendency of participants to sway slightly), the measurement was recorded photographically. This procedure was repeated ten times for each participant. The combined weight measured on the two scales was compared to the true total weight measured on one scale to calculate the error in the method. Recording the measurement photographically for routine use of this method was impractical due to the problem of glare from the camera flash that frequently obscures the weight reading in the image. The following technique was therefore applied for the remainder of the study. Participants were weighed on one set of scales to measure their total weight. To account for the natural tendency for participants to sway slightly when standing still, the average of three random consecutive readings, recorded from the left hand side, was taken as representative of the participant's left side weight-bearing. The right measurement was calculated as the difference between left average weight-bearing and the participant's total weight. Measurements were taken with the researcher standing slightly behind the participant to minimise any influence on their balance (Figure 3.2). To assess the possible influence of the researcher's proximity to the participant, the average of three measurements was also recorded from the right side and compared to

the calculated result. (b) The technique described above was repeated ten times with repositioning after participants had walked across the room between measurements.

Fig.3.1 Participant standing astride two identical scales in a natural standing posture.

Fig.3.2. Participant measurement technique

2. (a) Group B measurements acquired at their baseline visit by DXA (GE Lunar Prodigy, Bedford, MA) from bilateral hip and total body scans were correlated with L/R WB measurements at baseline to assess whether any inequalities in L/R WB at this time point were associated with differences in L/R LLTM or BMD at the Total Hip or Neck of Femur (NOF). These regions were selected as they are most clinically relevant for the assessment of fracture risk. (b) L/R WB measurements were recorded in Group B by the dual-scales method at each of three visits at baseline, 6 months and 12 months.

3.3.3 *Statistical analysis*

The mean percentage difference between total weight measured on one scale and the combined weight distributed over two scales was calculated. The Intraclass Correlation Coefficient (ICC) between the right calculated and right recorded results, for Group A, was computed (SPSS version18.0). Short- and long-term consistency in L/R weight-bearing was calculated using the Root Mean Square Coefficient of Variation (RMSCV%) using the formula described by Gluer et al (250). Linear regression analysis (SPSS version18.0) was used to investigate relationships between left/right differences in weight-bearing and differences in BMD (at total hip & neck of femur sites) and LLTM from Group B results recorded at their first visit.

3.4 RESULTS

1. (a) The difference between total weight measured on one scale compared to dual-scales was 0.34%. The Intraclass Correlation Coefficient between right calculated and right recorded WB was 0.77 ($p<0.05$). (b) The mean percentage L/R WB for Group A was 50:50 and the short-term CV for L/R WB was 5.41%.

2. (a) Measurements of hip BMD and LLTM, at baseline for Group B, are shown in Table 3.2. No significant correlation was found in Group B between hip BMD differences and L/R WB at baseline. A weak, but statistically significant correlation of r=0.31 (p=0.047) was however found for differences in LLTM and L/R WB differences. (b) The mean percentage L/R WB at baseline for Group B was 51:49. The long-term CV for L/R WB in Group B was 7.01%.

Table 3.2. Group B DXA results at baseline visit

	Left	**Right**
	Mean (SD)	Mean (SD)
BMD (g/cm^2) - NOF	0.89 (0.13)	0.90 (0.13)
BMD (g/cm^2) - Total Hip	0.94 (0.15)	0.95 (0.15)
LLTM (kg)	6.34 (0.76)	6.31 (0.79)

SD: standard deviation

3.5 DISCUSSION

To assess the accuracy of two sets of identically calibrated scales to record the L/R distribution of total weight, it was necessary to establish that the combined weight measured whist standing astride two scales equalled the total weight measured conventionally on one scale. A photographic method was employed because the digital readout of the scales was highly sensitive to minor participant movements and it was therefore impossible to simultaneously read both digital readouts visually. The small amount of measurement error (0.34%) indicates that this is an accurate method. This photographic method is not however practical for routine use as the digital readout from the scale can often be obscured in the image due to glare from the camera flash. For this reason, having established that the dual scales are accurately measuring the distribution of total weight, an alternative visual method was adopted. To allow for the natural side-

to-side sway of participants whilst standing on the scales, three consecutive readings were taken from the left-hand side and the average of these calculated as representative of weight-bearing on that side. The right side was calculated as the difference between the left side average weight-bearing and the participant's total weight (recorded on one set of scales). It should be stressed that the equipment used in this study were very high quality 'bathroom style' scales with large flat surfaces and no protruding dials as shown in Figure 1. Participants were therefore able to place their feet on the scales in any position without adapting their normal stance. The efficacy of this method may not therefore be applicable to scales of a different design or poorer quality.

An individual's perception of 'personal space' is the area surrounding them within which they do not comfortably tolerate the proximity of a stranger (251), and it was therefore postulated that a participant's stance could be influenced by the proximity of the researcher with a tendency to move slightly towards or away from someone standing very close to them. This phenomenon was assessed by comparing the right side calculated result with the result recorded by the researcher standing on the right side. The ICC between the right calculated and right recorded results was $r = 0.77$ indicating that participants' balance was only minimally affected by the proximity of the researcher.

To establish the short-term consistency of L/R WB tendencies, Group A participants were re-measured ten times after walking across the room and returning to stand on the scales. Their results demonstrated a short-term CV of 5.41% indicating that there is a small amount of short-term inconsistency/variation in participants L/R WB tendencies. The long-term CV over three visits at six month intervals for Group B was 7.01%

indicating a degree of L/R WB variation comparable to the short-term CV in a general population sample represented by Group A. As Group B participants were already engaged in time consuming data collection sessions for the main study, it was not considered appropriate to burden them with the further activity required to assess their short-term variation in L/R WB tendencies. Figure 3.3 shows the left side weight-bearing variation of individual participants in Group B over the 12 month period and although a number of participants demonstrated considerable long-term variation in their weight-bearing, most showed a consistent tendency to bear more weight on a particular side.

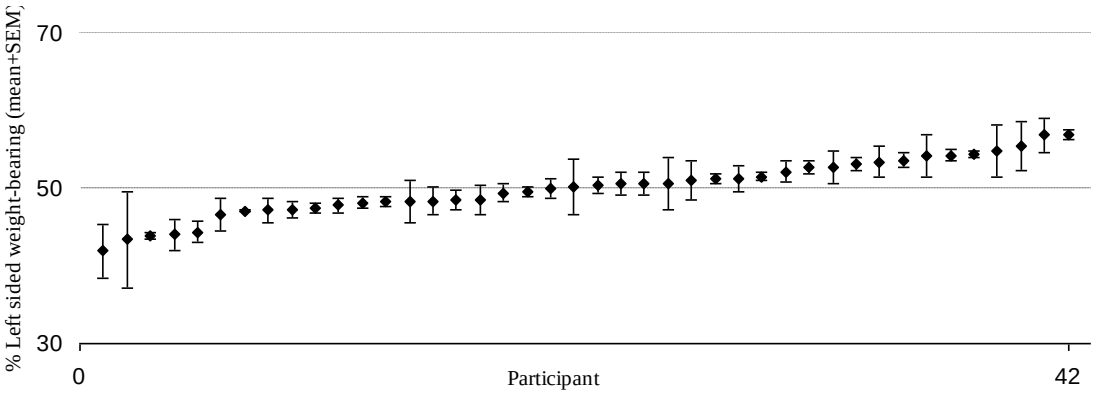


Fig.3.3. Group B – Left sided weight bearing, mean of 3 visits, expressed as percentage of total weight-bearing for individual participants (n=42)

As participants from both Group A and B were fully mobile with no recent history of lower limb injury, it was not expected that either would demonstrate any notable difference in their left/right weight-bearing. Whilst a number of individuals exhibited large differences between their left and right weight-bearing, the percentage means for groups A & B were 50:50 and 49:51 respectively. It was therefore not anticipated that

significant differences would be apparent in the Group B left/right measures of BMD and this was confirmed by the results. A small but statistically significant correlation was however found for differences in LLTM and L/R WB differences. The reason for this result is unclear. Whilst evidence from the literature suggests that any deficit in LLTM or BMD is attributable to reduced mechanical loading, it could also be feasible that weight-bearing inequalities are the result of unilaterally reduced muscle mass. In a study of healthy young adults, Hoffman et al (252) found no difference in unilateral postural stability between the functionally dominant and non-dominant lower limbs and therefore leg dominance (comparable to left or right-handedness) is not thought to account for these side-to-side differences. Leg dominance was not however investigated in this study.

In populations sustaining lower limb injury or surgery, it is possible for the range of unilateral weight-bearing to be 0-100% over the period from injury to full remobilization, potentially resulting in marked changes bilaterally in BMD & LLTM during the course of recovery. Although Group B participants had no history of leg or ankle fracture, 11 participants reported previous unilateral leg pathology, and 3 bilateral. These injuries or disabilities ranged in severity from minor arthritis to a ruptured patella tendon, and in incidence from 18 months to 40 years previously. The mean percentage L/R WB of these participants as a sub-group was not however significantly different to the non-injured controls; 49:51 compared to 51:49 respectively.

Although the results in the current paper relate to a fully ambulatory population, in circumstances where injured participants use support from either walking sticks or crutches, weight bearing on their legs is measured by weighing them with the supports

resting on the adjacent floor in their normal standing, supported position. Relative left/right weight-bearing is then calculated as a percentage of their total unsupported weight. All participants in this study were able to provide an unsupported weight measurement.

The major limitation of this dual-scales technique is that it measures weight-bearing in an upright stance and this may not be representative of typical weight-bearing during other activities including walking. Participants frequently commented that they rarely stand in this forward facing upright posture and adopt a more casual stance when standing for long periods. This may be less applicable to patient populations whose injuries limit their postural flexibility. It is acknowledged that this dual-scales method can only provide limited postural information on L/R weight distribution and the accuracy of this method has not been compared to the same parameter as measured by alternative, more sophisticated methods; nor does this study attempt to infer any information regarding other parameters of gait or balance. This method, using scales of suitable quality, does however afford sufficient refinement to discriminate between the relatively minor L/R WB inequalities demonstrated by a normal/control population with the greater left/right differences likely to be exhibited in patient populations affected by leg injuries or surgery. It has the advantage of being safe, easy to use and relatively inexpensive compared to alternative methods for weight-bearing assessment using equipment such as force plates or accelerometers.

3.6 CONCLUSION

The results demonstrate that total weight distributed over dual scales accurately reflects total weight measured on one scale, and this is an effective method for evaluating

weight distribution through the legs in a natural standing posture. The posture of participants was only minimally affected by the proximity of the researcher when recording the measurements. The short- and long-term L/R WB tendencies in Groups A and B respectively showed a similar level of variation. In a healthy postmenopausal population, inequalities in L/R WB were not associated with any significant L/R differences in BMD at the hip, but were weakly correlated with L/R differences in leg muscle mass.

CHAPTER 4. EVALUATION OF 1.5 TESLA MRI FOR MEASUREMENT OF CORTICAL BONE AND MUSCLE

4.1 INTRODUCTION

This chapter investigates the efficacy of 1.5 Tesla MRI scanning for the measurement of cortical bone and muscle size at the proximal femur, in sub-groups from the main study of control participants and newly fractured patients treated by plaster of Paris (POP).

DXA is the current gold standard for measuring a range of bone and muscle parameters including bone area, areal density, and regional lean tissue mass. It does not however differentiate between cortical and trabecular bone compartments. This can only be done effectively *in vivo* with CT imaging but this methodology has limitations both clinically and for research purposes due limited availability and the high radiation doses associated with CT examinations. A 1.5 Tesla Philips Intera MRI scanner is available at the research centre where the main study was conducted which afforded an opportunity to assess the use of MRI to directly measure the thickness of cortical bone and muscle mass at the proximal femur, and to monitor changes in these measurements over a period of twelve months.

4.2 AIMS AND OBJECTIVES

The objective of this aspect of the study was to assess the precision of repeat measurements, performed at various cortical bone and muscle sites at the proximal femur, from images obtained by 1.5 Tesla MRI in various planes and scan modes, and

to compare these to the measurement precision of bone and muscle parameters obtained by DXA scanning.

4.3 BRIEF METHODS & STATISTICS

The methods are described in full in Chapter 2. Section 2.3.2 details the methods for analyzing the scan images. Scans were performed using the protocols and sequences described in Table 2.6 with measurements taken at the sites shown in Table 2.8 and Figure 2.9. Volunteer subgroups from the main study were selected for MRI scanning at the same intervals as their DXA scans. Due to contraindications to MRI scanning i.e. the presence of new prosthetics or metallic components used in internal fixation of fracture, recruitment was limited to the control group and those newly fractured patients who had been treated by plaster of Paris only.

- Raw data acquired from the MRI scanner were downloaded in DICOM format onto DVD and imported as images to Apple Macintosh hardware using OsiriX v.3.9.4 software to analyse the images.
- Due to unavoidable tilt and rotation in patient positioning on the scanner, a given slice (either coronal or axial) did not always provide comparable anatomy on left and right sides of the body, as demonstrated in Fig 4.1. It was therefore necessary to use subjective judgement to select different slices providing the appropriate anatomical view on the right and left sides from which measurements could be taken.

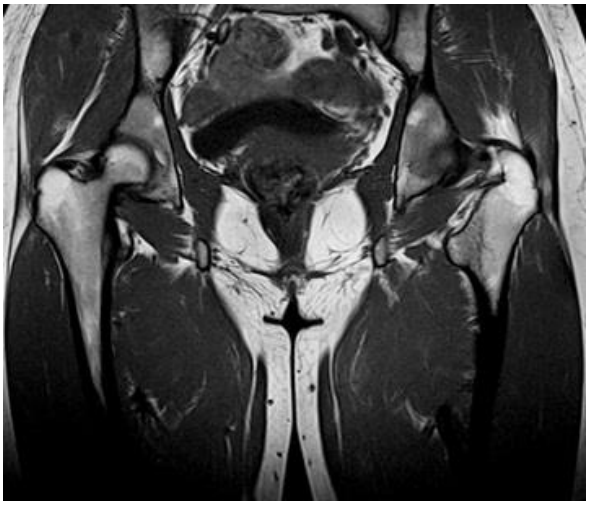


Figure 4.1 Coronal slice through the pelvis demonstrating unequal anatomical views on right and left sides due to tilt and rotation in the body position.

- It was important that slice selection should be consistent and as accurate as possible as the measurement criteria involved using levels at fixed distances from selected bone landmarks. The bone landmarks selected were the mid-femoral neck and the superior aspect of the greater trochanter. Slices were selected where the superior aspect of the greater trochanter was most prominently demonstrated in the image.
- The measurement levels were selected at fixed distances from the bone landmarks as shown in Table 2.8 and Figure 2.9. As it was only intended to compare changes in individuals over time and not to compare the exact equivalent anatomical position between individuals, these distances were the same for all participants regardless of their height or femur length. The distances of 9 cm and 14 cm were selected as appropriate sites at which to take measurements based on the anatomy of a participant whose overall height represented the mean for the original sample. Measurements were taken at the

selected levels, perpendicular to the endosteal bone surface at the femoral neck or shaft.

- Measurements were performed by two newly graduated medical imaging students from the University of Exeter. Both operators jointly assessed the appropriate slice from which to take measurements whilst a single individual performed all measurements to avoid inter-operator variability.
- Measurements were attempted on the images obtained by the STIR TSE coronal and PDW SPAIR axial sequences but poor visual definition of the boundaries between tissues did not allow satisfactory analysis.
- The coronal sections of the T1W TSE sequences were analysed initially because locating the bone landmarks, to identify the relevant slice, was more readily achieved than on the axial slices. Bone landmarks are difficult to pinpoint on axial slices as the differences in bone geometry at different levels is not obvious. Correctly locating equivalent slices either on left and right sides of the body, or on repeat scans, is highly subjective or requires precise calculation. This is a time-consuming exercise and as the precision results from the coronal sections were shown to be very poor, it was not considered to be a worthwhile use of time resources to proceed with analysis of the axial sections; therefore only the results from the T1W TSE coronal sections are reported in the results.
- Precision of repeat MRI measurements was compared to that of repeat DXA measured parameters of BMD, bone area and muscle mass acquired at the same time points as the MRI scans.
- Descriptive statistics were used for sample means and standard deviations in participant characteristics and measurements at Visit 1 (Microsoft Excel 97-2003). Precision error in measurements, over three visits at six month intervals,

was calculated using the Root Mean Square Coefficient of Variation (RMSCV%) using the formula described by Glüer et al (253). The correlation between right and left side measurements at Visit 1 was calculated using paired samples correlation (SPSS version18.0).

4.4 RESULTS

4.4.1 SAMPLE

A total of eleven controls and two fracture participants volunteered for the MRI study. A participant recruitment and retention summary is shown in Table 2.3 (Chapter 2). Two control participants were lost to the MRI element of the study because they were unable to enter the scanner due to claustrophobia. Four scanning sessions could not be completed at Visit 4 due to postponement of appointments by participants and unavailability of the MRI scanner at the rescheduled dates. Poor recruitment rates and the low number of fracture patients treated by POP alone, resulted in only two participants from Group 3 undertaking the MRI element of the study. As no meaningful conclusions about long-term changes in bone and muscle parameters would be available from the limited number of Group 3 participants completing the study, it was excluded from the final analysis. Poor image quality and anatomical irregularities in the scans for one control participant made measurement too arbitrary to be useful. Ultimately the data for 5 control participants only, who completed the whole study, were analysed.

4.4.2 DESCRIPTIVES

Table 4.1. Participant characteristics at Visit 1 - means and standard deviations (n=5)

	Mean	SD
Age (yrs)	72.6	9.9
Weight (kg)	64.6	13.2
Height (m)	1.6	0.1
Body Mass Index ($kg.m^{2)}$	24.9	4.8

Table 4.2 MRI measurements at Visit 1 (cm) - means and standard deviations (n=5)

	Right		Left	
	Mean	SD	Mean	SD
Site 1	0.40	0.24	0.29	0.14
Site 2	0.64	0.80	0.22	0.05
Site 3	0.41	0.15	0.35	0.10
Site 4	0.40	0.15	0.44	0.19
Site 5	0.58	0.17	0.55	0.20
Site 6	0.55	0.15	0.63	0.18
Site 7	2.96	0.45	3.01	0.48
Site 8	7.93	0.65	7.77	0.41
Site 9	3.26	0.56	3.36	0.40
Site 10	7.22	1.19	6.99	1.58

Table 4.3 DXA measurements at Visit 1 - means and standard deviations (n=5)

	Right		Left	
	Mean	SD	Mean	SD
BMD NOF ($g/cm^{2)}$	0.81	0.10	0.79	0.12
BMD Total Hip ($g/cm^{2)}$	0.84	0.19	0.83	0.19
BMD Femoral shaft (g/cm)	0.99	0.24	1.00	0.27
Area NOF ($cm^{2)}$	5.05	0.28	5.11	0.61
Area Total Hip (cm^2)	30.76	2.43	30.69	3.52
Area Femoral shaft (cm^2)	13.92	0.34	13.51	0.39
Lean leg tissue (g)	5976	436	5816	327

4.4.3 PRECISION ERROR

Table 4.4 Measurement variation (RMSCV%) over three visits - Coronal Sections T1W TSE

	RIGHT CV%	LEFT CV%
Site 1	37.0	37.3
Site 2	18.5	40.2
Site 3	23.7	36.9
Site 4	15.6	17.9
Site 5	12.7	11.1
Site 6	13.6	13.9
Site 7	6.8	8.4
Site 8	2.3	3.6
Site 9	6.7	10.2
Site 10	7.3	8.2

Table 4.5 Measurement variation (RMSCV%) over three visits - DXA ROIs (n=5)

	RIGHT CV%	LEFT CV%
BMD NOF	2.08	2.15
BMD Total Hip	1.48	1.34
BMD Femoral shaft	2.09	1.55
Area NOF	1.96	0.54
Area Total Hip	0.09	1.21
Area Femoral shaft	0.56	0.73
Lean leg tissue	1.83	2.98

4.4.4 CORRELATION BETWEEN RIGHT AND LEFT SIDE MEASUREMENTS

Table 4.6 Correlation coefficient between right and left measurements at Visit 1 - MRI (n=5)

Site 1: Cortical bone - Lateral, perpendicular to Mid femoral neck	0.35	
Site 2: Cortical bone - Medial, perpendicular to Mid femoral neck	0.90	*
Site 3: Cortical bone - Lateral, 9 cm inferior to superior aspect of greater trochanter	0.58	
Site 4: Cortical bone - Medial, 9 cm inferior to superior aspect of greater trochanter	0.98	*
Site 5: Cortical bone - Lateral, 14 cm inferior to superior aspect of greater trochanter	0.97	*
Site 6: Cortical bone - Medial, 14 cm inferior to superior aspect of greater trochanter	0.50	
Site 7: Vastus lateralis muscle - Lateral, 9 cm inferior to superior aspect of greater trochanter	0.91	*
Site 8: Medial muscle compartment 9 cm inferior to superior aspect of greater trochanter	0.95	*
Site 9: Vastus lateralis muscle - Lateral, 14 cm inferior to superior aspect of greater trochanter	0.40	
Site 10: Medial muscle compartment 14 cm inferior to superior aspect of greater trochanter	0.73	

* Significant at 95% level

Table 4.7 Correlation coefficient between right and left measurements at Visit 1 - DXA (n=5)		
BMD NOF	0.98	*
BMD Total Hip	0.97	*
BMD Femoral shaft	0.98	*
Area NOF	0.50	
Area Total Hip	0.86	
Area Femoral shaft	0.16	
Lean leg tissue	0.87	

* Significant at 95% level

4.5 DISCUSSION

When considering the potential of MRI to measure changes in cortical bone and muscle mass, it is first necessary to establish the true changes in bone and muscle parameters in the study sample as measured by alternative reliable methods. DXA is an established modality for the measurement of BMD, bone area and muscle mass. The short term precision error at the NOF and Total Hip sites for the DXA scanner used in this study was shown to range between 0.85% and 2.00% depending on the BMI category of the participants (229). The study inclusion criteria selected postmenopausal females only and these would be expected to lose approximately 1% BMD over a twelve month period (100). The final data analysis was limited to the control participants and it was not anticipated that any significant changes in bone parameters would occur in this group over a one year period beyond the expected bone loss typically observed in postmenopausal women. The results from the DXA scans (Table 4.5), performed at the same time points as the MRI scans, demonstrate minimal variation with RMSCV% ranging from 0.54 (Area NOF) to 2.98 (Lean Leg Tissue). As these are in the same order of magnitude as the short-term precision error of the equipment, it is inferred that minimal change is occurring in the true values of the measured parameters. Whilst the

parameters measured by DXA are different to those in the MRI study, the low long-term variation in DXA results suggests that minimal variation would also be expected in direct measurement of cortical bone and muscle width using MRI. Results from the MRI measurements (Table 4.4), nevertheless demonstrate considerably higher RMSCV% at all sites with the exception of the medial muscle compartment (Site 8). RMSCV% range from 2.3% (Site 8) to 40.2% for cortical bone thickness at the medial aspect of the mid-femoral neck (Site 2). The highest variation occurs in measurement of the cortices at the femoral neck where the width dimensions are very small. The voxel size used in the acquisition of the MRI data was 1.97/2.11/5.00 mm. As the mean width of the cortices at Sites 1&2 are estimated to be in the range of 0.22 to 0.64 cm (Table 4.2) i.e. only two to three pixels in width, a high percentage in measurement error at this resolution would be expected. This is due largely to partial volume effects whereby more than one tissue type can be present within a single voxel. In this situation the greyscale value attributed to that voxel will be averaged and the boundary at the interface of two tissue types will be indistinct resulting in inaccurate measurement. This will not be a significant source of measurement error where the dimensions of the tissue are of greater magnitude and it is evident that the precision error for the cortical widths at the femoral shaft (Sites 3-6) are of a lower order, and lower still for the muscle mass at Sites 7-10. Nonetheless, the differential is very large between the RMSCV% at MRI measurement sites and the RMSCV% in DXA measurements. This suggests that this method is imprecise and whilst it may provide approximate values for the dimensions of tissue at the measured sites, repeat measurements are unreliable for monitoring long-term change.

Problems with this method include difficulties in identifying the correct slice for measurement analysis, particularly on axial sections. There is a high degree of subjectivity in both the measurement process and locating equivalent slices in repeat scans using specific bone landmarks. Further sources of measurement error arise as a result of difficulties in the reproducing the exact participant positioning for the follow-up scans. Small amounts of rotation and tilt of the limbs and torso are unavoidable and will vary to some extent upon repositioning causing variation in the way that tissues lay relative to the scan planes. Scans are performed in a supine position that causes soft tissue to compress and spread such that measurement variation could occur between repeat scans after repositioning even without any true difference in tissue mass or dimensions having occurred. This issue of repositioning accuracy is however also applicable to DXA scanning. When comparing the correlation between left and right side measurements using MRI and DXA (Tables 4.6 & 4.7), a comparable level of correlation is demonstrated in both methods suggesting that measurement error due to positioning is similar for both modalities and that selection of the appropriate MRI slices, for left and right analysis, was performed correctly and to an acceptable standard.

The study was limited by the low number of data sets ultimately available for analysis; however the available data were adequate to provide a preliminary assessment of the utility of this technique.

The width of cortical bone at the femoral head is minimal and trabecular bone forms the bulk of bone volume at the Total Hip sites measured by DXA. The cortical tissue effectively forms a skin in these regions & separation of the cortical and trabecular components would make minimal difference to BMD measurements for diagnostic

purposes. Nevertheless, appositional growth and changes in cortical width may impact on the geometric properties of the femur affecting fracture risk. It would be valuable for research purposes to be able to monitor these changes as a result of disuse using a modality that is safe, readily available and acceptable to study participants. Further work could be valuable to assess the efficacy of this method using higher image resolution to achieve greater accuracy and precision.

4.6 CONCLUSION

Results from the DXA scans, show minimal variation in measurements of bone and muscle parameters over a 12 month period and the CVs are of comparable magnitude to the precision error of the equipment, even before allowing for an expected loss of approximately 1% BMD in female postmenopausal participants. Although measuring different parameters to those assessed by MRI, the DXA results suggest that only minimal change in bone and muscle mass is occurring in the control sample. In contrast, large variation is demonstrated in the parameters measured by MRI that are inconsistent with the DXA results suggesting that this variation is primarily due to large measurement precision errors resulting from inadequate image resolution and ambiguity in interpreting the MRI images. In conclusion, repeat 1.5 Tesla MRI T1W TSE coronal scan images, at the resolutions used in this study, may be useful for approximating the dimensions of cortical bone and muscle at the proximal femur but do not afford sufficient accuracy and reliability to be valid for monitoring change.

CHAPTER 5. RESULTS – MEDICAL AND LIFESTYLE HISTORY RELATING TO BONE HEALTH, AND LONGITUDINAL CHANGES IN FUNCTIONAL AND TREATMENT PARAMETERS

5.1 INTRODUCTION AND AIMS

This chapter presents the results relating to the medical and lifestyle history of participants, relevant to their bone health at baseline. Longitudinal changes in levels of activity, function, weight-bearing, pain, treatments, therapies and health perceptions are reported. The chapter aims to evaluate differences between groups of postmenopausal women who have had periods of immobilisation due to leg injury or surgery. Three groups; newly fractured patients, patients with fractures from more than one year previously, and total knee replacement patients are compared to an age matched control group.

5.2 OBJECTIVES

- To describe participant characteristics at baseline.
- To assess risk factors for compromised bone health at baseline and to compare differences between groups.
- To assess changes in parameters of activity, function, weight-bearing, pain levels, treatments, therapies and health perceptions over a twelve month period and to compare these between groups.
- To investigate the relationship between physical function and parameters of recovery.

5.3 BRIEF METHODS AND & STATISTICS

The methods are described in detail in Chapter 2, section 2.2.3. Statistical methods are described in Chapter 2, section 2.3.4.

5.4 RESULTS

5.4.1 PATIENT CHARACTERISTICS AND HISTORY RELATING TO BONE HEALTH

Table 5.1 Participant characteristics at baseline - visit 1 (Means/SD)

	Controls			TKR			#<3wks			#>1yr		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Age (yrs)	43	**64.7**	7.7	19	**66.1**	6.9	9	**62.6**	7.2	24	**65.3**	8.3
Weight (kg) at visit 1	43	**68.3**	10.2	19	**83.1**	16.1 **	9	**71.0**	11.1	24	**74.3**	15.8
Height (m) at visit 1	43	**1.6**	0.1	19	**1.6**	0.1	9	**1.7**	0.1	24	**1.6**	0.1
BMI at visit 1	43	**25.4**	3.2	19	**32.2**	7.1 **	9	**26.1**	3.8	24	**28.4**	5.5 *
BMI at age 21	39	**22.0**	2.6	18	**23.0**	3.4	9	**22.1**	3.1	23	**21.8**	3.7
Menarche age (yrs)	43	**12.9**	1.6	19	**13.0**	1.7	9	**12.1**	1.2	24	**13.3**	1.7
Menopause age (yrs)	41	**50.2**	4.8	19	**48.3**	6.3	9	**47.9**	6.2	23	**49.1**	4.9
HRT use (months)	21	**54.2**	55.3	12	**69.6**	76.9	6	**56.1**	68.8	9	**44.9**	42.8
OCP use (months)	31	**92.0**	78.4	17	**95.6**	84.9	7	**79.2**	141.7	11	**114.7**	106.3
Alcohol consumption (level 1 -5)	43	**2.7**	1.5	19	**1.7**	1.3 *	9	**2.0**	0.7 *	24	**2.0**	1.4
Caffeine consumption (level 1 -5)	43	**1.0**	0.6	19	**1.1**	0.6	9	**1.2**	0.4	24	**1.2**	0.5
Exercise 6 months pre-baseline (level 1 -5)	43	**2.3**	0.7	19	**1.3**	0.9 **	9	**2.4**	0.7	24	**2.0**	1.0
Number of other supplements taken#	43	**1.1**	1.6	19	**0.9**	1.4	9	**1.2**	1.1	22	**0.5**	0.6 *
Years as smoker	16	**19.4**	13.5	5	**8.2**	3.0 **	3	**25.7**	15.9	6	**19.5**	10.5

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

Notes:

SD =standard deviation

Alcohol consumption levels : 1 = social only, 2= 1-5, 3=6-10, 4=11-15, 5=16-20, 6=>21 units per day

Caffeine consumption levels: 1=1-5, 2=6-10, 3=11-15 cups per day

Exercise levels: 1-<0.5, 2=0.6-1, 3=>1 hour per day

 # Dietary supplements other than calcium, vitamin D or multivitamin

Table 5.2 Participant characteristics at baseline - visit 1 (percentages of group).

	Controls		**TKR**		**#<3wks**		**#>1yr**	
	n	%	n	%	n	%	n	%
White Caucasian ethnicity	43	**100**	19	**100**	9	**100**	24	**100**
Patients wearing plaster cast	43	**0**	19	**0**	9	**100**	24	**0**
Current smoker	43	**0**	19	**0**	9	**0**	24	**4**
Previous Total Knee Replacement	43	**0**	19	**32**	9	**0**	24	**0**
Previous Total Hip Replacement	43	**0**	19	**11**	9	**0**	24	**0**
Relative with hip/spine/wrist fracture	42	**37**	18	**26**	9	**11**	24	**38**
Relative with other fracture	42	**35**	19	**32**	9	**44**	24	**46**
Relative with osteoporosis	43	**19**	18	**5**	9	**11**	24	**21**

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

Table 5.3 Participant characteristics at baseline- visit 1 - Non parametric variables (Median/interquartile)

	Controls n=43			**TKR n=19**			**#<3wks n=9**			**#>1yr n=24**			
	Median	25th Centile	75th centile	Median	25th Centile	75th centile	Median	25th Centile	75th centile	Median	25th Centile	75th centile	
Total co-morbidities directly relating to bone health.	**1.0**	0.0	1.0	**1.0**	1.0	2.0	**0.0**	0.0	1.0	**1.0**	0.0	1.0	*
Total of all co-morbidities	**1.0**	0.0	2.0	**2.0**	2.0	4.0	**1.0**	0.0	2.0	**1.0**	1.0	2.0	*
Previous fractures.	**0.0**	0.0	1.0	**0.0**	0.0	1.0	**1.0**	0.0	1.0	**1.0**	0.0	2.0	*
Total number of fractures including baseline fracture.	**0.0**	0.0	1.0	**0.0**	0.0	1.0	**1.0**	0.0	1.0	**2.0**	1.0	3.0	*
Number of children.	**2.0**	1.0	3.0	**2.0**	1.0	3.0	**2.0**	1.0	3.0	**2.0**	1.3	3.0	

* **Independent Samples Median Test.** Null hypothesis: The medians of the parameter are the same across the groups. Null hypothesis rejected. Significance level 0.05

Table 5.4 Participant history of medical conditions relating to bone health (percentages of group).

	Controls		TKR			#<3wks		#>1yr	
	n	%	n	%		n	%	n	%
Rheumatoid arthritis	43	**2.3**	19	**15.8**		9	**0.0**	24	**0.0**
Osteoarthritis	43	**27.9**	19	**84.2**	**	9	**22.2**	24	**29.2**
Ankylosing spondylitis	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**
Diabetes	43	**2.3**	19	**10.5**		9	**0.0**	24	**0.0**
Hyperthyroid	43	**0.0**	19	**0.0**		9	**0.0**	24	**4.2**
Hypothyroid	43	**9.3**	19	**21.1**		9	**0.0**	24	**12.5**
Cancer Breast	43	**7.0**	19	**0.0**		9	**11.1**	24	**0.0**
Other cancer	43	**7.0**	19	**10.5**		9	**0.0**	24	**12.5**
Paget's disease	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**
Liver disease	43	**2.3**	19	**0.0**		9	**0.0**	23	**0.0**
Kidney disease	43	**4.7**	19	**0.0**		9	**0.0**	24	**8.3**
Gastric pathology	43	**2.3**	19	**0.0**		9	**11.1**	24	**8.3**
Lactose Intolerance	43	**4.7**	19	**0.0**		9	**0.0**	24	**0.0**
Cohn's disease	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**
Coeliac disease	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**
Irritable bowel syndrome	43	**9.3**	19	**10.5**		9	**0.0**	24	**12.5**
Malabsorption	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**
Osteomalacia	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**
Bulimia	43	**0.0**	19	**5.3**		9	**0.0**	24	**0.0**
Anorexia	43	**0.0**	19	**5.3**		9	**0.0**	24	**4.2**
Hysterectomy	43	**16.3**	19	**21.1**		9	**22.2**	24	**12.5**
Oophrectomy (1 or 2)	42	**14.3**	18	**5.6**		9	**33.3**	23	**8.6**

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

Table 5.5 Participant history of medications and dietary supplements relating to bone health (percentages of group).

	Controls		TKR			#<3wks		#>1yr	
	n	%	n	%		n	%	n	%	
Steroids	43	**4.7**	19	**10.5**		9	**0.0**	24	**4.2**	
Anticonvulsants	43	**0.0**	19	**5.3**		9	**22.2**	24	**0.0**	
Diuretics	43	**9.3**	19	**26.3**		9	**11.1**	23	**17.4**	
Chemotherapy	43	**2.3**	19	**0.0**		9	**0.0**	24	**0.0**	
Immunosuppressive agents	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**	
Heparin	43	**2.3**	19	**5.3**		9	**0.0**	24	**4.2**	
Thyroxin	43	**9.3**	18	**27.8**		9	**0.0**	23	**17.4**	
Didronel	43	**0.0**	19	**0.0**		9	**0.0**	24	**4.2**	
Fosamax	43	**2.3**	19	**10.5**		9	**0.0**	24	**29.2**	*
Calcitonin	43	**0.0**	18	**11.1**		9	**0.0**	24	**25.0**	*
Actonel	43	**0.0**	19	**0.0**		9	**0.0**	24	**16.7**	*
Teriparatide	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**	
Protelos	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**	
Pamidronate	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**	
Zolendronate	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**	
Ibandronate	43	**0.0**	19	**0.0**		9	**0.0**	24	**0.0**	
Fluoride	43	**2.3**	19	**0.0**		9	**0.0**	24	**0.0**	
Multi vitamin	42	**23.8**	19	**57.9**	**	9	**22.2**	22	**4.5**	*
Calcium	42	**28.6**	19	**10.5**		9	**11.1**	22	**50.0**	
Vitamin D	42	**19.0**	19	**10.5**		9	**11.1**	22	**40.9**	

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

5.4.2 FUNCTIONAL AND TREATMENT PARAMETERS AT BASELINE AND LONGITUDINAL CHANGES

The following figures 5.1 to 5.7 depict the parameters where the greatest changes were observed during the study period. Significances of differences between groups and of changes within groups over the study period are reported in Tables 5.6 and 5.8.

Figure 5.1. Changes in ipsilateral weight-bearing

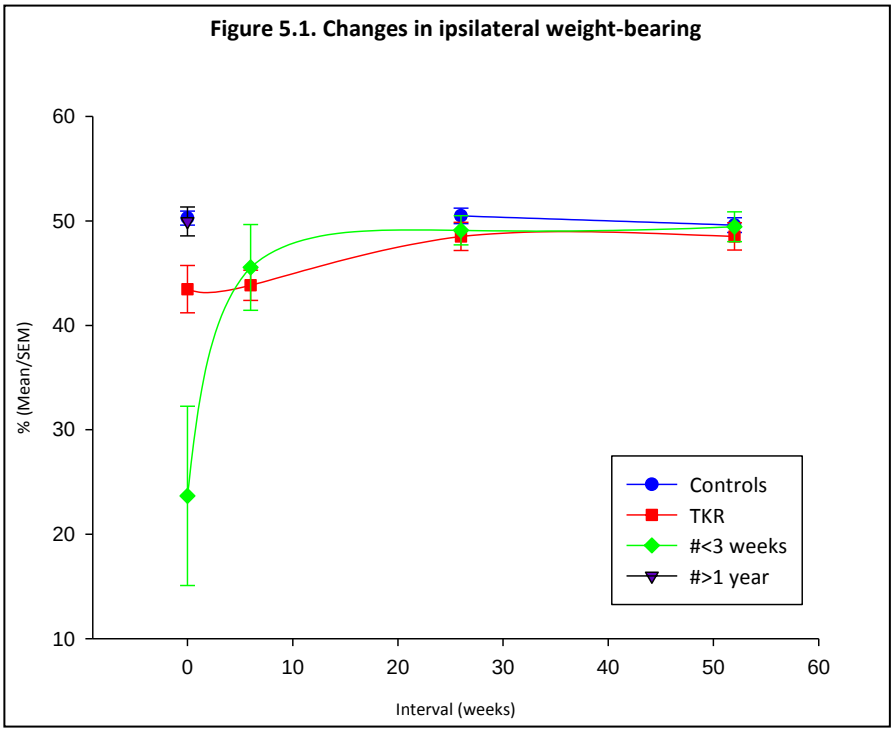


Figure 5.2. Changes in function scores (LEFS)

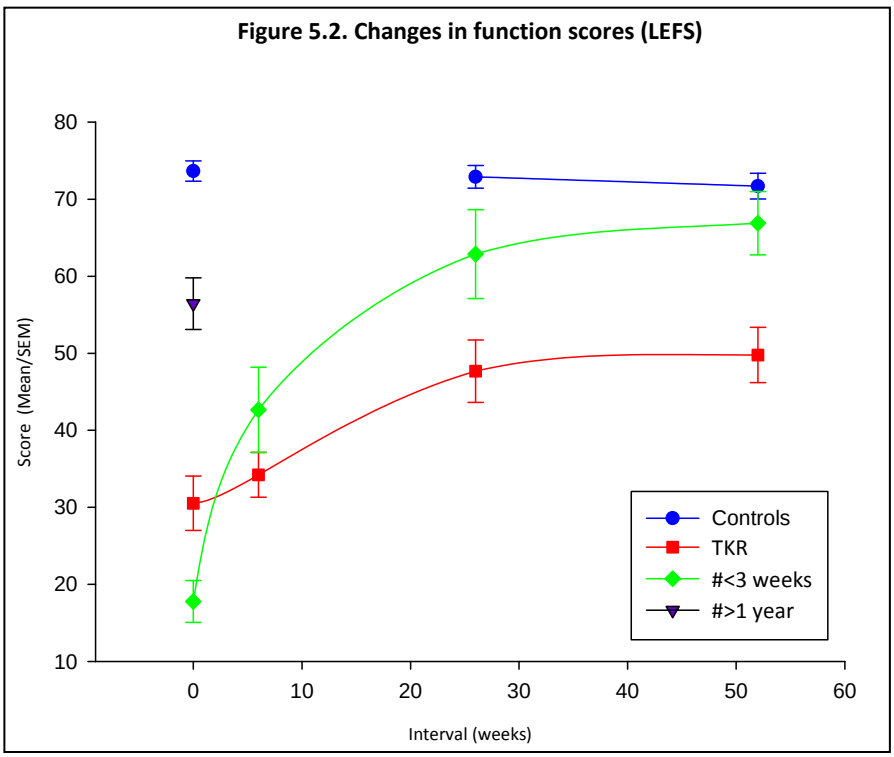


Figure 5.3. Changes in perceived health scores (EQ5D)

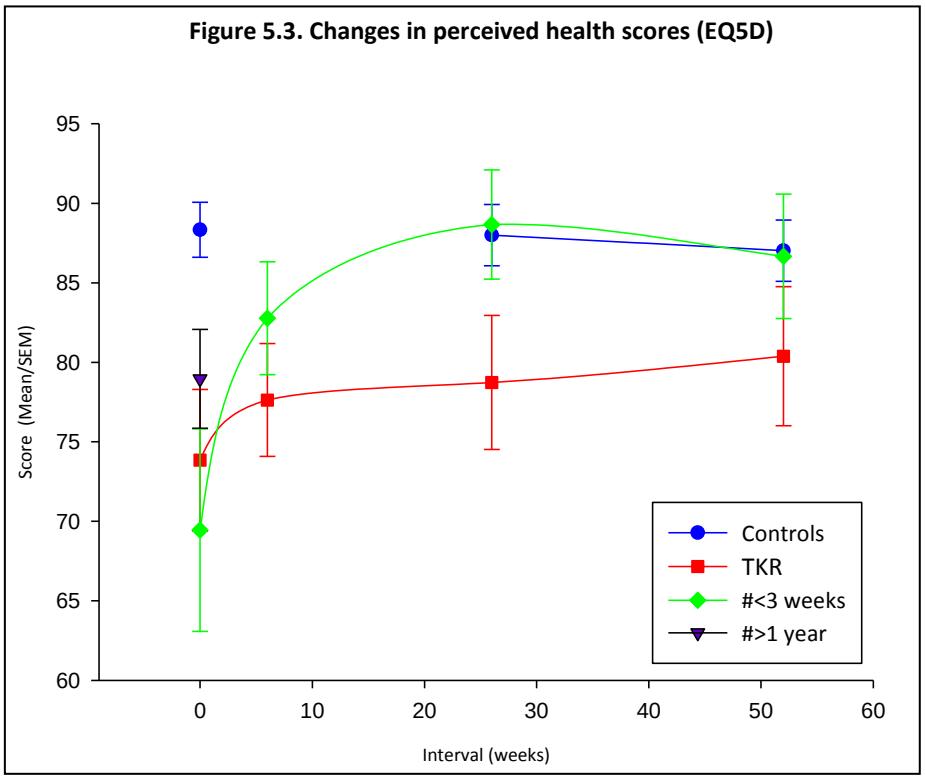


Figure 5.4. Changes in pedometer readings

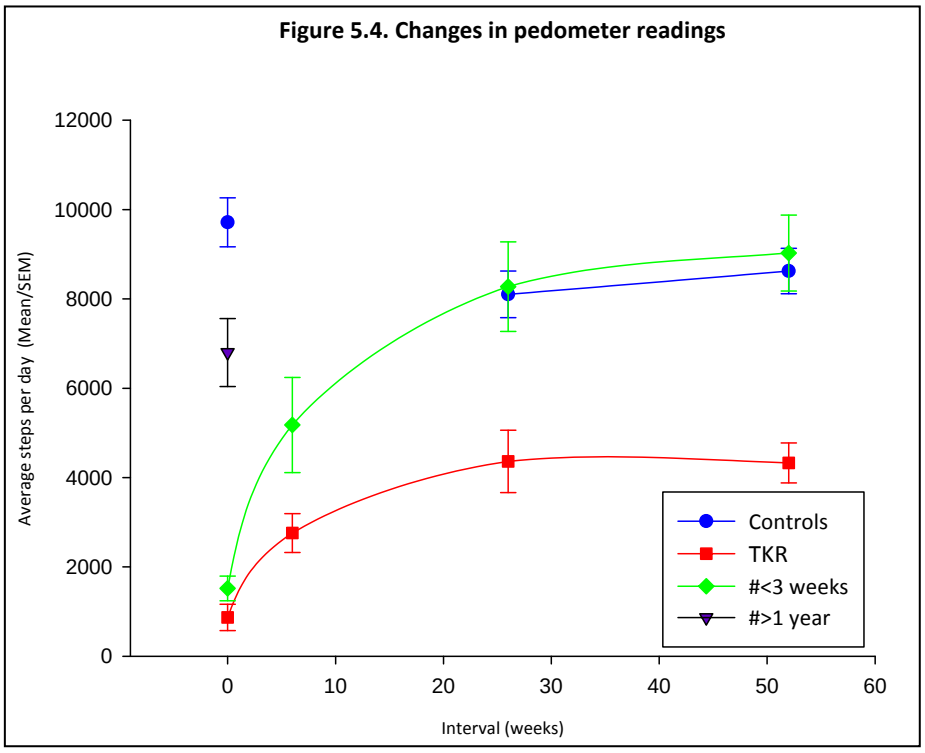


Figure 5.5. Changes in activity scores (IPAQ)

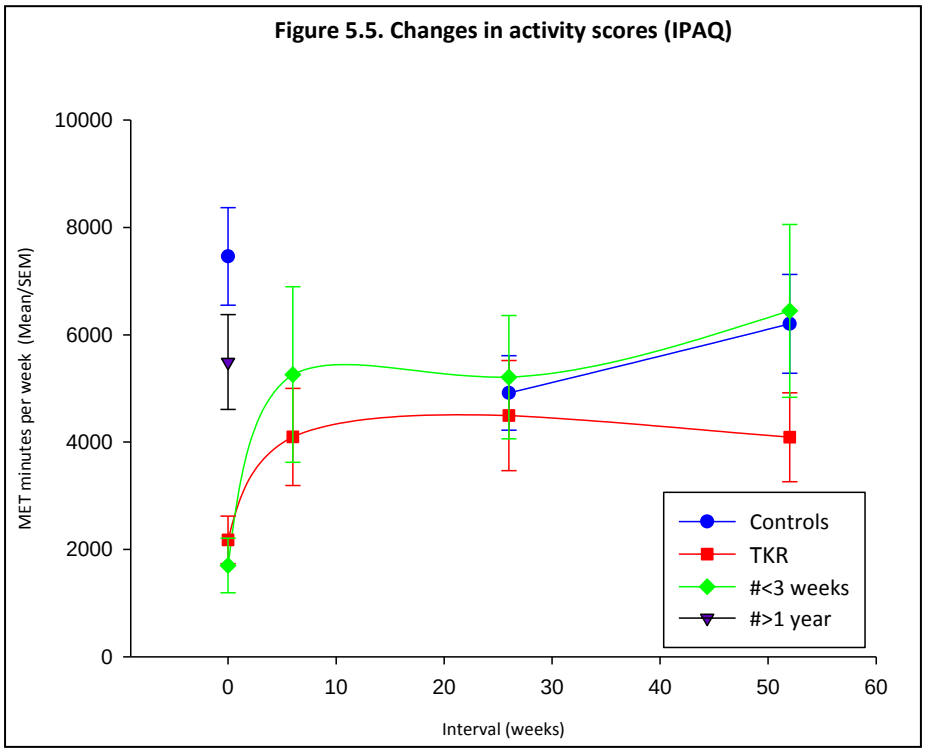


Figure 5.6. Changes in sitting scores (IPAQ)

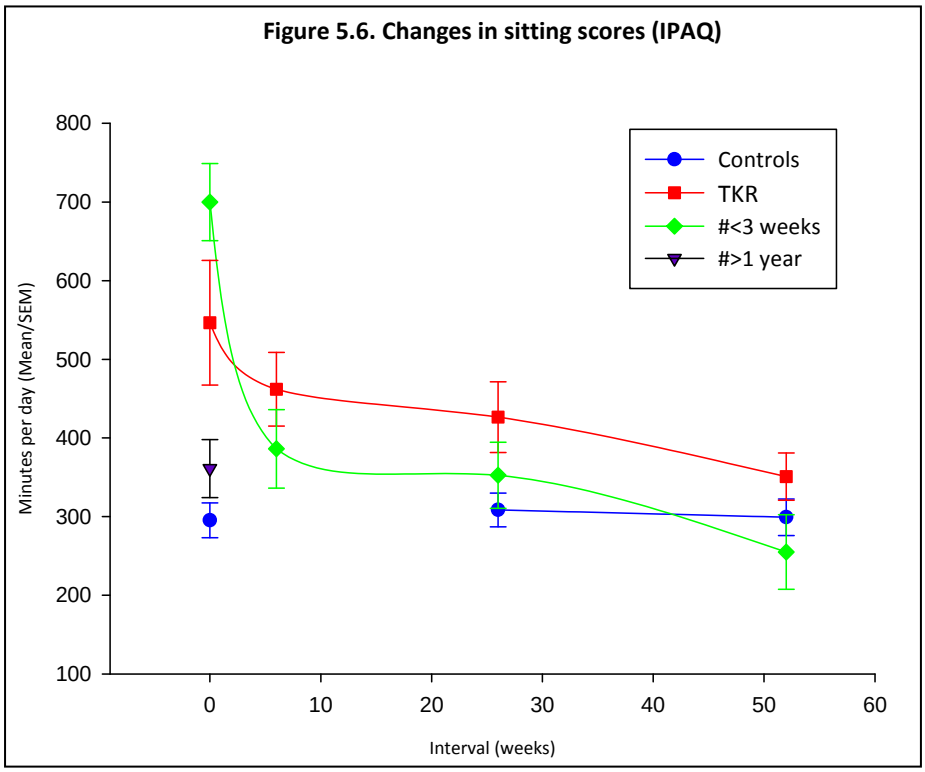


Figure 5.7. Changes in pain VAS

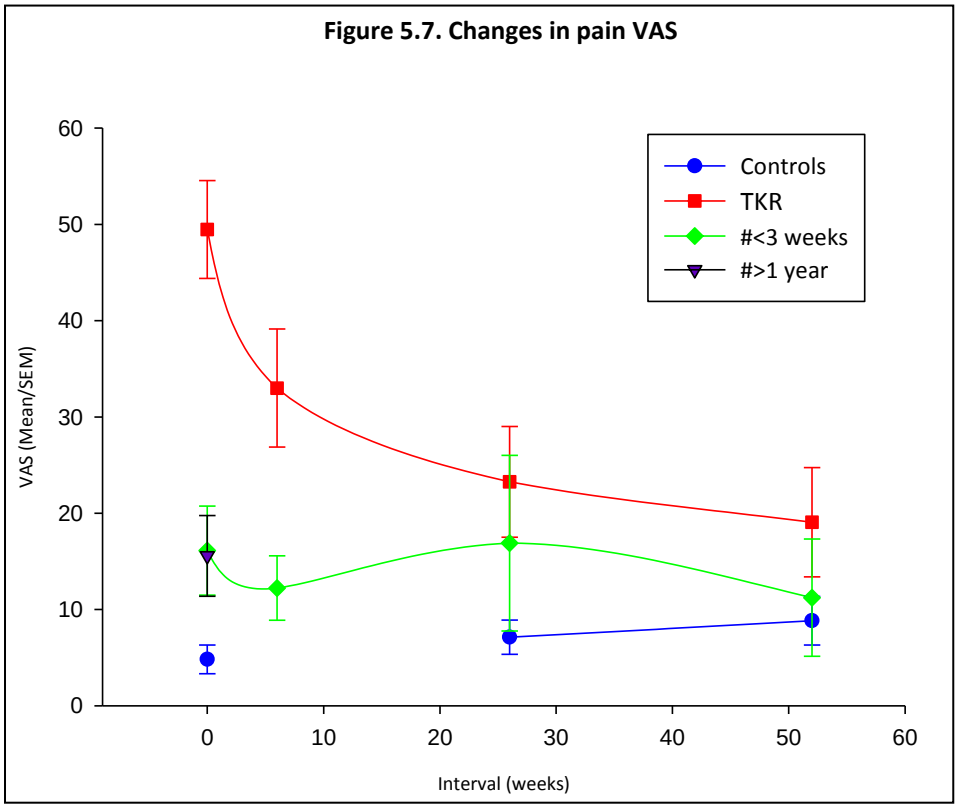


Table 5.6 Changes in functional parameters - (Means/SD)

	Controls			TKR				#<3wks				#>1yr			
	n	Mean	SD	n	Mean	SD		n	Mean	SD		n	Mean	SD	
Weight (Kg) at visit 1	43	**68.3**	10.2	19	**83.1**	16.1	**	9	**71.0**	11.1		24	**74.3**	15.8	
Weight (Kg) at visit 2	0			19	**82.5**	16.9		9	**71.5**	10.8		0			
Weight (Kg) at visit 3	43	**68.3**	9.8	19	**84.2**	17.5	**	9	**71.8**	11.2		0			
Weight (Kg) at visit 4	43	**68.3**	10.0	19	**85.1**	18.4	**	9	**72.1**	11.0		0			
Height (m) at visit 1	43	**1.6**	0.1	19	**1.6**	0.1		9	**1.7**	0.1		24	**1.6**	0.1	
Height (m) at visit 2	0			19	**1.6**	0.1		9	**1.7**	0.1		0			
Height (m) at visit 3	43	**1.6**	0.1	19	**1.6**	0.1		9	**1.6**	0.1		0			
Height (m) at visit 4	43	**1.6**	0.1	19	**1.6**	0.1		9	**1.6**	0.1		0			
BMI at visit 1	43	**25.4**	3.2	19	**32.2**	7.1	**	9	**26.1**	3.8		24	**28.4**	5.5	*
BMI at visit 2	0			19	**31.7**	7.2	†	9	**26.3**	3.9		0			
BMI at visit 3	43	**25.4**	3.0	19	**32.5**	7.5	**	9	**26.4**	3.9		0			
BMI at visit 4	43	**25.4**	3.1	19	**32.7**	7.8	**	9	**26.6**	3.6		0			
% Ipsilateral weight-bearing at visit 1	43	**50.2**	4.4	19	**43.5**	9.9	**	9	**23.7**	25.7	*	24	**49.9**	6.8	
% Ipsilateral weight-bearing at visit 2	0			19	**43.8**	6.3		9	**45.6**	12.3	††	0			
% Ipsilateral weight-bearing at visit 3	43	**50.5**	4.9	19	**48.5**	5.9	†	9	**49.1**	4.2	†	0			
% Ipsilateral weight-bearing at visit 4	43	**49.6**	4.6	19	**48.5**	5.7	†	9	**49.4**	4.3	†	0			
% Contralateral weight-bearing at visit 1	43	**49.8**	4.4	19	**55.7**	11.3	*	9	**67.3**	27.4		24	**49.6**	6.2	
% Contralateral weight-bearing at visit 2	0			19	**55.8**	6.6		9	**51.3**	14.0	†	0			
% Contralateral weight-bearing at visit 3	43	**49.5**	4.9	19	**51.5**	5.9		9	**50.9**	4.2		0			
% Contralateral weight-bearing at visit 4	43	**50.6**	4.6	19	**51.5**	5.7		9	**49.4**	3.3		0			

LEFS Score at visit 1	43	**73.7**	8.6		19	**30.5**	15.4	**		9	**17.8**	8.2	**		24	**56.5**	16.4	**
LEFS Score at visit 2	0				19	**34.2**	12.7			9	**42.7**	16.6		††	0			
LEFS Score at visit 3	43	**72.9**	9.7		19	**47.7**	17.7	**	††	9	**62.9**	17.3		††	0			
LEFS Score at visit 4	43	**71.7**	11.0		19	**49.8**	15.7	**	††	9	**66.9**	12.3		††	0			
EQ-5D Health state VAS at visit 1	42	**88.3**	11.3		19	**73.8**	19.4	**		9	**69.4**	19.1	**		24	**79.0**	15.3	**
EQ-5D Health state VAS at visit 2	0				19	**77.6**	15.5			9	**82.8**	10.6		†	0			
EQ-5D Health state VAS at visit 3	43	**88.0**	12.6		19	**78.7**	18.4	*		9	**88.7**	10.3		††	0			
EQ-5D Health state VAS at visit 4	42	**87.0**	12.6		18	**80.4**	19.1		†	9	**86.7**	11.7		†	0			
Average pedometer steps at visit 1	41	**9716**	3596		17	**870**	1283	**		9	**1517**	830	**		21	**6801**	3731	**
Average pedometer steps at visit 2	0				19	**2757**	1895			9	**5178**	3201		††	0			
Average pedometer steps at visit 3	41	**8104**	3415	††	19	**4361**	3046	**	††	9	**8277**	3009			0			
Average pedometer steps at visit 4	40	**8626**	3329	†	15	**4327**	1950	**	††	9	**9029**	2549			0			
IPAQ (MET-minutes/week) at visit 1	40	**7461**	5963		10	**2178**	1932	**		3	**1701**	1526	*		19	**5492**	4339	
IPAQ (MET-minutes/week) at visit 2	0				16	**4097**	3948			7	**5260**	4911			0			
IPAQ (MET-minutes/week) at visit 3	38	**4917**	4559	††	17	**4493**	4478			8	**5211**	3451		†	0			
IPAQ (MET-minutes/week) at visit 4	40	**6206**	6032	†	13	**4091**	3617			8	**6448**	4830			0			

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

†p=<0.05 when compared to baseline for the same group

††p=<0.01 when compared to baseline for the same group

SD =standard deviation

Table 5.7 Changes in treatment and functional parameters (percentages of group).

	Controls			TKR			#<3wks			#>1yr		
	n	%		n	%		n	%		n	%	
Full mobility at visit 1	43	**100.0**		19	**36.8**	**	9	**0.0**		24	**95.8**	
Full mobility at visit 2	0			19	**10.5**		9	**0.0**		0		
Full mobility at visit 3	43	**97.7**		19	**52.6**	**	9	**66.7**	††	0		
Full mobility at visit 4	43	**93.0**		17	**76.5**	†	9	**100.0**		0		
Receiving physical therapy at visit 1	43	**0.0**		19	**42.1**		9	**0.0**		24	**0.0**	
Receiving physical therapy at visit 2	0			19	**94.7**	††	9	**77.8**	††	0		
Receiving physical therapy at visit 3	43	**4.7**		19	**52.6**	**	9	**22.2**		0		
Receiving physical therapy at visit 4	43	**7.0**		19	**31.6**	*	9	**22.2**		0		
Receiving prescribed calcium at visit 1	43	**0.0**		19	**0.0**		9	**0.0**		24	**12.5**	
Receiving prescribed calcium at visit 2	0			19	**5.3**		9	**22.2**		0		
Receiving prescribed calcium at visit 3	43	**7.0**		19	**5.3**		9	**22.2**		0		
Receiving prescribed calcium at visit 4	43	**9.3**	†	19	**10.5**		9	**22.2**		0		
Receiving bisphosphonate + Ca at visit 1	43	**2.3**		19	**10.5**		9	**0.0**		24	**33.3**	*
Receiving bisphosphonate + Ca at visit 2	0			19	**10.5**		9	**0.0**		0		
Receiving bisphosphonate + Ca at visit 3	43	**14.0**	†	19	**10.5**		9	**22.2**		0		
Receiving bisphosphonate + Ca at visit 4	43	**16.3**	†	19	**15.8**		9	**22.2**		0		
Using pain-killers for baseline injury at visit 1	43	**0.0**		18	**55.6**		9	**66.7**		24	**4.2**	
Using pain-killers for baseline injury at visit 2	0			19	**84.2**	†	9	**33.3**		0		
Using pain-killers for baseline injury at visit 3	42	**0.0**		19	**42.1**	**	9	**11.1**		0		
Using pain-killers for baseline injury at visit 4	43	**0.0**		19	**26.3**	*	9	**11.1**		0		

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

†p=<0.05 when compared to baseline for the same group

††p=<0.01 when compared to baseline for the same group

Table 5.8 Changes in functional parameters - Non parametric variables (Median/interquartile)

	Controls n=43			TKR n=19			#<3wks n=9			#>1yr n=24			
	Median	25th Centile	75th centile	Median	25th Centile	75th centile	Median	25th Centile	75th centile	Median	25th Centile	75th centile	
Previous number of falls (not inc. baseline injury)	**0.00**	0.00	0.00	**0.00**	0.00	0.00	**0.00**	0.00	0.50	**0.00**	0.00	0.00	
Number of falls between visit 1&2				**0.00**	0.00	0.00	**0.00**	0.00	0.00				
Number of falls between visit 2&3	**0.00**	0.00	0.00	**0.00**	0.00	0.00	**0.00**	0.00	0.00				
Number of falls between visit 3&4	**0.00**	0.00	0.00	**0.00**	0.00	1.00	**0.00**	0.00	0.00				
Pain VAS at visit 1	**0.00**	0.00	5.00	**50.00**	30.00	70.00	**10.00**	7.50	20.00	**8.00**	0.00	25.00	*
Pain VAS at visit 2				**35.00**	5.00	55.00	**10.00**	2.50	20.00				
Pain VAS at visit 3	**0.00**	0.00	10.00	**10.00**	5.00	50.00	**1.00**	0.00	40.00				*
Pain VAS at visit 4	**1.00**	0.00	10.00	**9.00** †	0.00	28.75	**0.00**	0.00	25.00				
PHQ-9Total score at visit 1	**1.00**	0.00	3.00	**4.00**	1.00	6.00	**2.00**	1.00	8.00	**2.50**	0.00	6.50	
PHQ-9Total score at visit 2				**6.00**	1.00	9.00	**3.00**	0.50	3.50				
PHQ-9Total score at visit 3	**1.00**	0.00	4.00	**1.00**	0.00	8.00	**2.00**	0.50	4.50				
PHQ-9Total score at visit 4	**1.00**	0.00	4.00	**3.00** †	1.00	6.00	**0.00**	0.00	6.00				
PHQ-9 Difficulty score at visit 1	**1.00**	0.00	1.25	**1.00**	1.00	2.00	**1.00**	1.00	2.00	**1.00**	0.00	1.75	
PHQ-9 Difficulty score at visit 2				**2.00**	1.00	2.00	**1.00**	0.50	2.00				
PHQ-9 Difficulty score at visit 3	**1.00**	0.00	1.00	**1.00**	0.00	1.00	**1.00**	0.50	1.00				
PHQ-9 Difficulty score at visit 4	**1.00**	0.00	1.00	**1.00** †	1.00	1.00	**0.00**	0.00	1.50				
GAD-7 Total score at visit 1	**1.00**	0.00	3.00	**2.00**	1.00	7.00	**1.00**	0.00	5.00	**1.00**	0.00	4.00	
GAD-7 Total score at visit 2				**2.00**	0.00	4.00	**1.00**	0.00	4.00				
GAD-7 Total score at visit 3	**0.00**	0.00	3.00	**1.00**	0.00	3.00	**0.00**	0.00	3.00				
GAD-7 Total score at visit 4	**0.00**	0.00	3.00	**2.00**	0.00	6.00	**0.00**	0.00	3.00				
GAD-7 Difficulty score at visit 1	**1.00**	0.00	1.00	**1.00**	0.00	2.00	**1.00**	0.00	1.50	**1.00**	0.00	1.00	
GAD-7 Difficulty score at visit 2				**1.00**	0.00	2.00	**1.00**	0.00	2.00				
GAD-7 Difficulty score at visit 3	**0.00**	0.00	1.00	**1.00**	0.00	1.00	**0.00**	0.00	1.00				
GAD-7 Difficulty score at visit 4	**0.00**	0.00	1.00	**1.00**	0.00	1.00	**0.00**	0.00	1.00				

*** Independent Samples Median Test. Null hypothesis: The medians of the parameter are the same across the groups. Null hypothesis rejected. Significance level 0.05**

† **Related-Samples Friedman's Two-way Analysis of Variance by Ranks.** Null hypothesis: The distributions of the parameter across the four visits are the same. Null hypothesis rejected. Significance level 0.05

5.4.3 RELATIONSHIP BETWEEN PHYSICAL FUNCTION AND PARAMETERS OF RECOVERY

Stepwise multiple regression analysis was performed to create a model for each group with significant explanatory factors for the dependent variable of physical function (LEFS). Models were created at baseline (visit 1) and two time points during recovery, 6 months (visit 3) and 1year (visit 4). LEFS was selected as the dependent variable because return to optimal function is a key outcome measure of physical recovery and a marker of quality of life. The independent variables added into the model were:

EQ5D Health state VAS

Ipsilateral weight-bearing

Pain VAS

Pedometer average steps per day

Number of co-morbidities relating to bone health

Total of all co-morbidities

Number of falls in the preceding 6 months (or since last visit)

Physical therapy

Age

BMI

Number of knee replacements

PHQ9 Total score

GAD7 Total score

The resulting model summaries for each time point are shown in Tables 5.9 to 5.11 and reported below:

VISIT 1

Table 5.9. Model Summary: Dependent variable LEFS at Baseline (visit 1)

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
TKR	1	.625[a]	.391	.350	12.387
#>1yr	1	.685[b]	.469	.439	11.358
	2	.777[c]	.603	.557	10.098

a. Predictors: (Constant), Pedometer Average visit 1
b. Predictors: (Constant), Pain VAS 1
c. Predictors: (Constant), Pain VAS 1, Age Scan1

Controls: No significant independent variables found.

TKR: Model 1 was an acceptable fit describing 39.1% of variance in LEFS (R^2_{adj}= 35%), statistical significance $F_{1,15}$= 9.62, p=0.007. With other variables held constant, function level (LEFS) was positively related to pedometer scores, increasing by 0.007 points for every extra step (t=3.10, p=0.007).

LEFS = 25.192 + 0.007 pedometer steps (Eq.5.1)

#<3 weeks: No significant independent were variables found.

#>1yr: Model 2 was a good fit describing 60.3% of variance in LEFS (R^2_{adj}= 55.7%), statistical significance $F_{2,17}$= 12.93, p=0.000. With other variables held constant, function level (LEFS) was negatively related to pain scores and age, decreasing by 0.622 points for every extra point on the pain scale (t= -4.88, p=0.000) and 0.721 points for every extra year in age (t= -2.40, p=0.028).

LEFS = 111.467 – 0.622 pain – 0.721 age (Eq.5.2)

VISIT 3

Table 5.10. Model Summary: Dependent variable LEFS at visit 3

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
Controls	1	.737[a]	.543	.531	6.561
TKR	1	.768[b]	.589	.565	11.652
#<3wks	1	.923[b]	.853	.831	7.106
	2	.983[c]	.966	.955	3.660
	3	.994[d]	.988	.981	2.368

a. Predictors: (Constant), EQ-5DHealth state VAS 3
b. Predictors: (Constant), Pain VAS 3
c. Predictors: (Constant), Pain VAS 3, EQ-5DHealth state VAS 3
d. Predictors: (Constant), Pain VAS 3, EQ-5DHealth state VAS 3, PHQ-9Total score 3

Controls: Model 1 was a good fit describing 54.3% of variance in LEFS (R^2_{adj}= 53.1%), statistical significance $F_{1,39}$= 46.28, p=0.000. With other variables held constant, function level (LEFS) was positively related to EQ5D health state scores, increasing by 0.547 points for every extra health point (t=6.80, p=0.000).

LEFS = 24.889 + 0.547 health state (Eq.5.3)

TKR: Model 1 was a good fit describing 58.9% of variance in LEFS (R^2_{adj}= 56.5%), statistical significance $F_{1,17}$= 24.41, p=0.000. With other variables held constant, function level (LEFS) was negatively related to pain, decreasing by 0.541 points for every extra point on the pain scale (t= -4.94, p=0.000).

LEFS = 60.270 - 0.541 pain (Eq.5.4)

#<3 weeks: Model 3 was an excellent fit describing 98.8% of variance in LEFS (R^2_{adj}= 98.1%), statistical significance $F_{3,5}$=140.85, p=0.000. With other variables held constant, function level (LEFS) was negatively related to pain scores, decreasing by 0.643 points for every extra point on the pain scale (t= -14.15, p=0.000), and positively related to EQ5D health scores and PHQ-9 depression scores, increasing by 0.919 points for every

extra health point (t= 6.62, p=0.001) and by 2.124 points for every extra depression point (t= 3.01, p=0.028).

LEFS = -13.608 + 0.919 health state - 0.0.643 pain + 2.124 depression (Eq.5.5)

#>1yr: Not applicable.

VISIT 4

Table 5.11. Model Summary: Dependent variable LEFS at visit 4

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
Controls	1	.488[a]	.238	.218	9.336
	2	.634[b]	.402	.369	8.387
#<3wks	1	.886[c]	.785	.754	6.113

a. Predictors: (Constant), Pain VAS 4
b. Predictors: (Constant), Pain VAS 4, Total all comorbidities
c. Predictors: (Constant), Age

Controls: Model 2 was an acceptable fit describing 40.2% of variance in LEFS (R^2_{adj}= 36.9%), statistical significance $F_{2,36}$= 12.09, p=0.000. With other variables held constant, function level (LEFS) was negatively related to pain scores and total number of co-morbidities, decreasing by 0.307 points for every extra point on the pain scale (t= 3.56, p=0.001) and 4.608 points for every additional co-morbidity (t= 3.14., p=0.003).

LEFS = 79.541 - 0.307 pain – 4.608 co-morbidities (Eq.5.6)

TKR: No significant independent variables found.

#<3 weeks: Model 1 was a very good fit describing 78.5% of variance in LEFS (R^2_{adj}= 75.4%), statistical significance $F_{1,7}$= 12.09, p=0.000. With other variables held constant, function level (LEFS) was negatively related to age, decreasing by 1.510 points for every extra year in age (t=5.05, p=0.001).

LEFS = 161.445 – 1.510 age (Eq.5.7)

#>1yr: Not applicable.

Table 5.12. Simplified summary of multiple regression analysis
Significant explanatory factors (from same visit) for LEFS

	Controls	TKR	#<3 wks	#>1yr
Visit 1		↑ pedometer		↓ pain ↓ age
Visit 2				
Visit 3	↑ EQ5D health	↓ pain	↓ pain ↑ EQ5D health ↑ PHQ-9 depression	
Visit 4	↓ pain ↓ co-morbidities		↓ age	

↑ indicates increase in LEFS score i.e. improvement in function as the score for the independent variable increases
↓ indicates decrease in LEFS score i.e. decline in function as the score for the independent variable increases

5.5 DISCUSSION

Baseline differences between groups:

The results (Tables 5.1 to 5.3) show that participants were well matched in age and menopause age. All participants were of white Caucasian ethnicity. The #<3weeks group had a lower age at onset of menarche, but this was not significant. The groups did not report significant differences in their BMI at age 21, but the TKR and #>1year groups had significantly higher BMI at the start of the study compared to the controls, (32.2±7.1, p=<0.01) and (28.4±5.5, p=<0.05) respectively. The high BMI for the TKR group, in the obese range as defined by the WHO criteria (254), is consistent with the fact that the main clinical indication for TKR is osteoarthritis, accounting for 94-97% of operations, and that the greatest risk factors for knee OA are age and obesity (255).

Nicholls et al (256) demonstrated that BMI at middle age is the strongest predictor for the necessity of TKR. The low BMI reported at age 21 (23.0±3.4), in the normal range, suggests that the TKR group was not originally at high risk for knee OA. Whilst it is probable that a substantial increase in BMI in later life is the major cause of OA in this group, it cannot be stated with any certainty that their current high BMI level is not the result of low levels of function and activity due to OA. The BMI at age 21 is however a self-reported, retrospective estimate and potential bias in participants' recollection should be considered. The TKRs reported significantly lower levels of exercise in the 6 months preceding the baseline visit (p=<0.01) with a mean of less than half an hour per day compared to half to one hour for the other groups, confirming that they had poorer levels of function and activity than the other groups for a protracted period prior to surgery.

All groups were comparable in their previous use of Hormone Replacement Therapy (HRT) and the Oral Contraceptive Pill (OCP) and all had a median of two children. Only one participant on the study was a current smoker from the #>1year group, and of those participants who were previous smokers, the TKR group smoked for significantly fewer years compared to the controls (p=<0.01). Caffeine consumption in the form of drinks such as coffee, tea and carbonated drinks was similar across the groups but alcohol consumption was lower in the TKRs (p=<0.05). With regard to family history, no significant differences were found between the groups for the number of immediate relatives who had sustained hip, spine or other fractures. Nor were there significant differences for relatives with osteoporosis. It should be noted however, that participants' awareness and recall of family history was often vague or incomplete. Participants were asked about their own history of fracture (excluding their current injury where

applicable) and the results showed significant differences between the groups with a median of 1 previous fracture for the #<3weeks and #>1year group compared to zero for the controls and TKRs. Fracture history included any fracture sustained at any age and due to any cause, and did not exclude traumatic and childhood injuries. This result is consistent with previous studies which demonstrate that previous fracture, at any site, is a risk factor for subsequent fractures, independent of BMD (257, 258).

Table 5.4 gives the results for participants' medical history of conditions that are known to have direct effects on bone health. The groups were well matched in this respect differing only in the incidence of osteoarthritis which was, as entirely expected, significantly higher (p=<0.01) in the TKR group where this pathology was the major contributor to the necessity for TKR surgery. Indeed, 32% of the TKRs presented at baseline with a previous TKR, and 11% with a previous contralateral total hip replacement. With regard to the total number of co-morbidities suffered by participants (including those relating to bone health), significant difference (p=<0.05) was demonstrated with the TKR group having a median of two co-morbidities compared to one for the other groups, indicating generally lower levels of fitness in this group. Table 5.5 summarises the use of medications known to impact on bone health, either positively or negatively, and again the groups were well matched with the notable exception of the #>1year group who were significantly higher users of bisphosphonate treatments (p=<0.05), prescribed calcium supplements and multivitamins but lower users (p=<0.05) of other supplements when compared to the controls.

The most marked differences between groups at baseline are evident in their levels of function. Whilst mean weight-bearing on the ipsilateral leg was close to 50% for the

controls and #>1year groups, it was obviously minimal (mean 23.7%) for the #<3weeks group who were all wearing a plaster cast at their first visit. The TKR group, who were seen before their surgery, demonstrated mean ipsilateral WB of 43.5%. Large differences were seen between levels of function measured by LEFS, which was indicative of the participants' ability to perform general daily activities. The control group mean score (73.7±8.6) was close to the maximum of 80, whereas the #>1year result was significantly poorer (56.5±16.4, p=<0.01), and the TKR and #<3weeks groups poorer still at (30.5±15.4, p=<0.01) and (17.8±8.2, p=<0.01) respectively. Activity in terms of pedometer readings of average steps per day, showed a similar pattern with the controls achieving levels close to the 10,000 steps per day (9716±3596) generally recommended for a healthy lifestyle (259). Readings were significantly lower for the #>1year (6801±3731, p=<0.01). As it was the intention to compare rates of recovery between groups, the TKR participants were asked to record pedometer readings for three days directly following surgery in order to be directly comparable to the #<3weeks group. As expected, readings were extremely low, 870±1283, p=<0.01, and 1517±830, p=<0.01 for TKR and #<3weeks respectively. Activity levels were also assessed by the self-reported IPAQ questionnaire which, whilst validated, is susceptible to a high degree of subjectivity and correlated poorly with activity measured by pedometer. The results for the group means nevertheless demonstrated the same pattern as pedometer activity (Fig. 5.5). These findings are reflected in the levels of mobility reported by participants. Thirty seven percent of TKRs regarded themselves as fully mobile at the pre-surgery visit (p=<0.01) whilst 4.2 % (n.s) of #>1year still did not consider themselves to be fully mobile. A large percentage of both TKRs (55.6%, n.s) and #<3weeks (66.7%, n.s) were taking painkillers at baseline and reported levels of pain were very high for the TKR group (median score 50/100). The median pain scores

were zero for the control group but similar for #<3weeks and #>1year at 10/100 and 8/100 respectively. Participants perceptions of their overall health state (not solely limited to their leg condition) conformed to the expected pattern, being best amongst the controls (88/100±11/100) and progressively lower (79/100±15/100, p=<0.01), (74/100±19.4/100, p=<0.01) and (69/100±19/100, p=<0.01) for the #>1year, TKR and #<3weeks groups respectively.

In addition to measures of physical recovery, mental wellbeing was also considered as both an explanatory variable for physical outcomes and as an outcome measure in its own right. This was assessed by the levels of depression and anxiety reported by the PHQ-9 and GAD-7 questionnaires. The results are presented in Table 5.8 but are fully described and analysed in chapter 7.

Longitudinal changes:

For all of the key functional parameters, there is a consistent picture of improvement throughout the period of the study, although the extent of recovery varies between the TKR and #<3weeks groups. Significant changes compared to baseline occurred in all of the following parameters of recovery at varying intervals over the one year study period. Figure 5.3 shows that the #<3weeks group return to 45.6±4.2% ipsilateral WB at visit 2 (p=<0.01) and are restored to the same levels as the controls by visit 3 (p=<0.05). The TKR group started from a higher baseline level than the fracture group but returned to similar levels of WB at the same time points. The LEFS scores (Fig.5.2) also followed the same trajectory with a progressive improvement in function returning to 66.9±12.3, p=<0.01, just below control levels for the #<3weeks group at the final visit. Whilst the TKR group also improved steadily, their function scores (49.8±15.7,

p=<0.01) remained well below the controls at visit 4. This pattern was repeated for activity levels measured by pedometer (Fig. 5.4) where #<3weeks participants returned to control levels at visit 3 (n.s) but TKRs improved to only 2757±1895 steps at visit 2(n.s) remaining at 4327±1950 (p=<0.01) steps at visit 4.

Pain scores (Fig. 5.7) improved rapidly for the TKRs (35/100, n.s) at visit 2, and 10/100 (n.s) at visit 3 but remained higher than the controls (9/100, p=<0.05) at visit 4. At visit 2, 84.2% of the TKR group were taking painkillers (p=<0.05) compared to baseline, but otherwise there were no significant changes in painkiller usage. Perceived health state (Fig 5.3) increased steeply (82.8±10.6, p=<0.05) for the #<3weeks group at visit 2, returning to control levels (88.7±10.3, p=<0.01) at visit 3, whilst the TKR group showed more gradual improvement culminating at 80.4±19.1 (p=<0.05) below control levels. Both TKRs and #<3weeks groups received some form of physical therapy throughout the study although the exact nature of this therapy varied considerably between patients, particularly for the TKRs for whom treatment could be a very minimal level of individual physiotherapy sessions, up to long term and regular gym sessions at the local hospital. However, at visit 2, 94.7% of TKRs and 77.8% of #<3weeks patients were receiving some form of physiotherapy, both p=<0.001 compared to baseline respectively. This had reduced to 31.6% and 22.2% at the final visit. It should be noted that physiotherapy did not always relate directly to the leg injury/surgery as patients frequently suffered pain elsewhere, particularly at the hips and shoulders and this was generally assumed by them to result from alterations in their posture or the use of crutches during recovery. All #<3weeks patients and 76.5% of TKRs reported a return to full mobility at the final visit. It was expected that the levels of function for the #>1year group would be comparable, if not considerably better than

for the #<3weeks patients at the end of the study. Surprisingly, whilst all #<3weeks patients reported a return to full mobility at the final visit, 4.2 % of #>1year still did not consider themselves to be fully mobile at a mean interval of 3.2±2.5 years after their injury. They also reported median pain scores above the level of the controls and similar to the baseline scores for #<3weeks group when they were experiencing pain immediately post trauma. Whilst the #<3weeks patients scored 66.9 points on the final LEFS score, (close to control levels at 71.7), this was only 56.5 for the #>1year group. The two fracture groups were similar in that they had a higher level of previous fractures than the other groups but, given that the #<3weeks group returned to normal levels of function and activity at the end of the study, it is unclear why long-term impairments should remain in the #>1yr group. It may be that the small sample available for the #<3weeks group has given misleading results or that the two fracture groups were not representative of comparable populations at the time when their fractures occurred. It is more probable that selection bias is responsible for the discrepancies between these two fracture groups. The difficulties in recruiting the newly fractured group have been described in chapter 2, section 2.1.5. Those subjects who were willing to participate, did so at some considerable inconvenience to themselves, particularly at the early stages of the study. They demonstrated a keen interest in research that overrode their difficulties in taking part; indeed three of the nine participants had occupational backgrounds in science and medicine and consequently had a clear understanding of the implications of the study. The Hawthorne effect is a well-known phenomenon in research whereby participants adapt their behaviour as a result of being observed (260). This may have affected participants in the newly fractured group causing them to optimise their recovery. For this reason, it is possible

that the results for this group are not typical of patients with leg fractures and results for the #>1yr group may be more representative of post leg fracture outcomes.

Falls history was recorded throughout this study but no significant differences were found between groups, or between visits. Osteoarthritis has been thought in the past to have a mitigating effect on fracture risk because it is associated high levels of BMD that are part of the pathogenesis of the disease (261). The incidence of low trauma fractures in OA patients has therefore been attributed to postural instability and either an increased occurrence or greater severity of falls (204, 206, 207). Whilst problems with stability can contribute to immobility, they can also, conversely, be the result of muscle atrophy and weakness due to immobility and chronic pain (79, 261). Results from a recent prospective multinational cohort study (GLOW) (262) on 51,386 postmenopausal women with self-reported OA, showed that that they experienced 25% more falls that those without OA, suggesting that this contributed to a 20% increased risk of fractures in these women. Although no significant differences were found in falls incidence between the groups on this study, group numbers were relatively small and participants may have been exercising increased caution following their surgery. This may have resulted in an underestimation the incidence of falls compared to a wider population with OA.

During the course of the study, numerous participants were diagnosed as osteopenic or osteoporotic and were prescribed either a calcium supplement or bisphosphonate plus calcium treatment as a result. The most significant increase in the number of participants put onto prescription was amongst the controls 9.3 % for calcium

supplement and 16.3% for bisphosphonate plus calcium at the end of the study, both p=<0.05 compared to baseline.

Relationship between physical function and parameters of recovery:

It is apparent that the multifactorial nature of physical and functional impairment following injury or surgery presents an unclear picture regarding the processes of recovery. In order to assess the significant variables involved in restoration of physical function measured by LEFS, a multiple regression analysis was performed and is summarised in Table 5.12. The results present a mixed selection of significant variables that influence LEFS in the different groups and at different stages. Nevertheless pain is the most frequently occurring explanatory variable causing a reduction in function as pain increases in all groups. In addition, fewer co-morbidities, lower age, higher health perception and increased pedometer activity all contribute to improved function amongst the groups. An increase in depression in the #<3weeks at visit 3 is shown to improve LEFS, contrary to expectations, but this may possibly be an aberrant result as participants were asked to give their responses to the PHQ-9 question relating to any reason and not limited to their leg problems.

Implications:

These results have implications for the treatment of patients following either fracture or surgery. Return to optimal levels of function is an important outcome measure of recovery as it enables patients to improve their quality of life and return to activities that they either engage in for pleasure or are demanded by their occupation. Although most significant explanatory variables for LEFS are unmodifiable, such as age and number of co-morbidities, others could be changed to hopefully effect an improvement in patient

outcomes. As expected, increased pain has been demonstrated to be a significant factor for reduced function. The TKR group has a complex range of problems associated with pain, beyond the trauma of surgery itself, which inhibits good levels of functional recovery. Obesity, which has been shown to be common in this group, is itself a predictor of higher levels of knee pain. This may not be solely related to increased mechanical loading on the joints, but may also involve obesity-related inflammatory mechanisms (263). Participants often expressed a reluctance to take or rely on painkillers, particularly if they were also taking a range of additional medications. This is reflected in the relatively low use of painkillers in the #<3weeks group at visit 2, although usage is substantially higher for the TKRs. Better, more appropriate pain relief might benefit patients and help them return more quickly to an active lifestyle. Higher pedometer scores were shown to improve LEFS for the TKR group. This may be the result of good surgical outcomes enabling patients to remobilize more quickly but it suggests that an early return to active exercise, as is already encouraged by medical practitioners, should be more rigorously encouraged following discharge from hospital. Overall, the results show the poorest functional outcomes for the TKR group and this is confirmed by Brandes et al (209) who monitored physical activity and health-related quality of life during the first year post TKR. They also found that the majority of patients did not achieve the levels of physical activity of healthy subjects 12 months post-surgery. Wylde et al (264) investigated the mid-term outcomes of TKR, 5 to 8 years post-operatively, and found that impairments persisted for TKA patients who experienced significantly greater functional limitations and pain levels than total hip replacement patients. Poorer long-term function, for both TKR and previous leg fracture patients, may also relate in part to ‘fear-induced activity limitation’ (265) or fear of falling, that inhibits a full return to normal activity. The range of physiotherapy services

available to patients in the study cohort was not consistent, with large variation in the rehabilitation programs that were offered. Patients from both fracture and TKR groups could benefit, in the short and long term, from strategies to improve their strength, balance and range of movement. Enhanced services for post-surgical exercise classes could assist patients to overcome psychological barriers to physical activity thereby reducing falls risk, mitigating bone and/or muscle loss and reducing the potential risk for future hip fracture. The group support afforded by such classes could also aid morale and encourage weight loss, potentially benefitting patients in their general health and recovery.

Limitations:

The study had several limitations, most notably the difficulties involved with recruitment and the potential for recruitment bias. The number of participants in the #<3weeks group was small due to the requirements of the study to attend data collection sessions close to the time of injury, and participants were generally limited to those with a strong support network of friends and relatives who could assist them with transport. The sample used in this study was 100% of white Caucasian ethnicity coming from a relatively affluent rural catchment area in the Southwest of England. The pedometer results suggest that the controls were a relatively active group for their age range and were frequently from backgrounds that afforded them the leisure to take part in the study. Although the socio-economic status of participants was not investigated, many, particularly amongst the control group, appeared to have backgrounds of relative affluence and good education that are generally associated with healthier lifestyles. Participants may not therefore be fully representative of the broader population which potentially limits the generalisability of the results. Other limitations included the

subjectivity of some of the questionnaires, particularly with regard to levels of pain and health state. Control participants were fairly consistent however in their longitudinal responses to these questionnaires, indicating a reasonable degree of precision. The IPAQ form, which was given to participants to complete at home, was difficult to complete for many people and had a poor response rate with many missing data. The correlation with activity measured by pedometer was very poor (r=33%) and it was not therefore included as an independent variable in the modeling. There were many potential and unavoidable confounders due to the nature of the pathologies under investigation, such as the presence of co-morbidities, previous knee replacements and treatments for low bone density that were prescribed during the course of the study. Where appropriate and relevant to the outcome measures, these were added as explanatory variables in the analysis.

5.6 CONCLUSION

It is evident that there are notable differences between the groups at baseline. The TKR group is distinct in their high mean BMI and poor general levels of function, health and activity relative to the controls. It is not known whether their high BMI, at obese level, is due to low levels of function and activity resulting from the disabling effects of osteoarthritis, or conversely, if high BMI was a contributory factor to the pathology that necessitated joint replacement. Despite showing an overall improvement in most areas of function and activity, the TKRs nonetheless fail to achieve the levels of the control group one year post surgery. The BMI for this group ranged from 21.4 to 51.5 $kg.m^2$ but, contrary to expectations, BMI was not a significant explanatory factor for

poor levels of function in this group. The newly fractured patients (#<3weeks) are significantly different to the controls at baseline in a number of key functional areas that are the inevitable consequence of the immobilization caused by their injury. They do however recover well and reasonably quickly in most key areas of functional recovery. Both fracture groups have a history of previous fracture rates higher than the controls. The group of participants who sustained their fracture more than one year ago, but within the past ten years (#>1year), exhibit distinct differences to both the controls and the newly fractured group. They differ from the other groups at baseline in significantly higher levels of bone sparing drug treatments and, relative to the controls, show significant impairment (p=<0.01) in scores for function, activity and perceived health state. These impairments do not persist at the end of the one year recovery period in the newly fractured group and it is not therefore clear why the #>1year should demonstrate long-term deficits in health and function in the longer term. The discrepancies between the two fracture groups may be a consequence of aberrant results due to the small number of participants in the #<3weeks group, but are potentially attributable to selection bias and the Hawthorne effect whereby behaviour may have been modified in the newly fractured participants, artificially optimising their recovery. The #>1year group may therefore be more representative of typical leg fracture patients than the newly fractured group.

More appropriate pain relief and an improved regime of physiotherapy and exercise, may help to improve patient outcomes following leg injury or TKR and may mitigate the long-term impairments demonstrated in the #>1yeargroup.

Future work:

Further work would be valuable to investigate whether improved pain relief and more consistently applied post-surgical exercise regimes, including group classes to encourage compliance, would be beneficial to the functional outcomes for both TKR and fracture patients in the immediate and long-term.

CHAPTER 6. RESULTS – DENSITOMETRY

6.1 INTRODUCTION AND AIMS

This chapter investigates the parameters of bone quantity, quality and geometry measured by densitometry, trabecular bone score (TBS) and advanced hip assessment (AHA). Body composition results derived from DXA total body scans are also assessed. The chapter aims to evaluate differences, at baseline and over a one year period of recovery, between groups of postmenopausal women, who have had periods of immobilisation due to leg injury or surgery. Three groups; newly fractured patients, patients with fractures from more than one year previously, and total knee replacement patients are compared to an age matched control group.

6.2 OBJECTIVES

- To describe differences between groups at baseline.
- To assess differences between ipsilateral and contralateral sides at baseline.
- To investigate differences between groups in longitudinal changes over a twelve month period in parameters of bone quantity, quality and geometry.
- To investigate differences between groups in longitudinal changes over a twelve month period in parameters of body composition.
- To investigate relationships between bone & body composition changes and functional, physical and emotional recovery.

6.3 BRIEF METHODS AND & STATISTICS

The methods are described in detail in Chapter 2, section 2.2.3. Statistical methods are described in Chapter 2, section 2.3.4.

6.4 RESULTS

6.4.1 PARTICIPANT CHARACTERISTICS

Participant characteristics are summarised in chapter 5, Tables 5.1 to 5.3.

6.4.2 DENSITOMETRY RESULTS AT BASELINE AND CHANGES OVER THE STUDY PERIOD

The following figures 6.1 to 6.22 depict the ipsilateral and contralateral bone and tissue measurements, expressed as group means and standard errors of the mean, where the greatest changes over the study period were observed. Significances of differences between groups and of changes within groups over the study period are reported in Tables 6.2 and 6.3.

Figure 6.1. Changes in BMD ai ipsilateral Neck of Femur

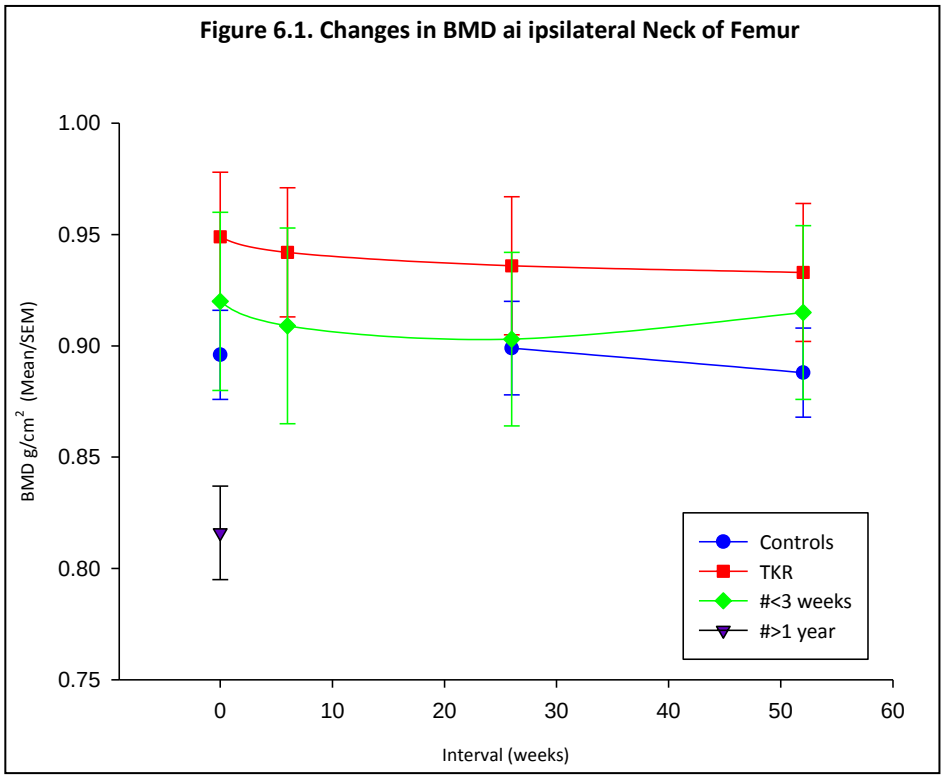


Figure 6.2. Changes in BMD at contralateral Neck of Femur

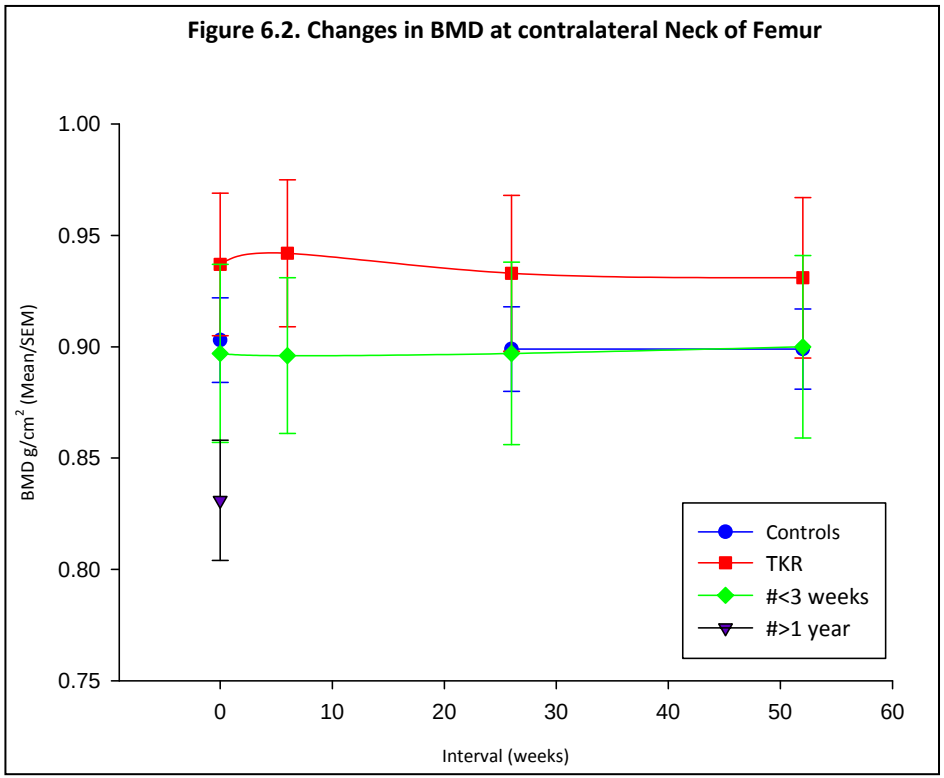


Figure 6.3. Changes in BMD at ipsilateral Total Hip

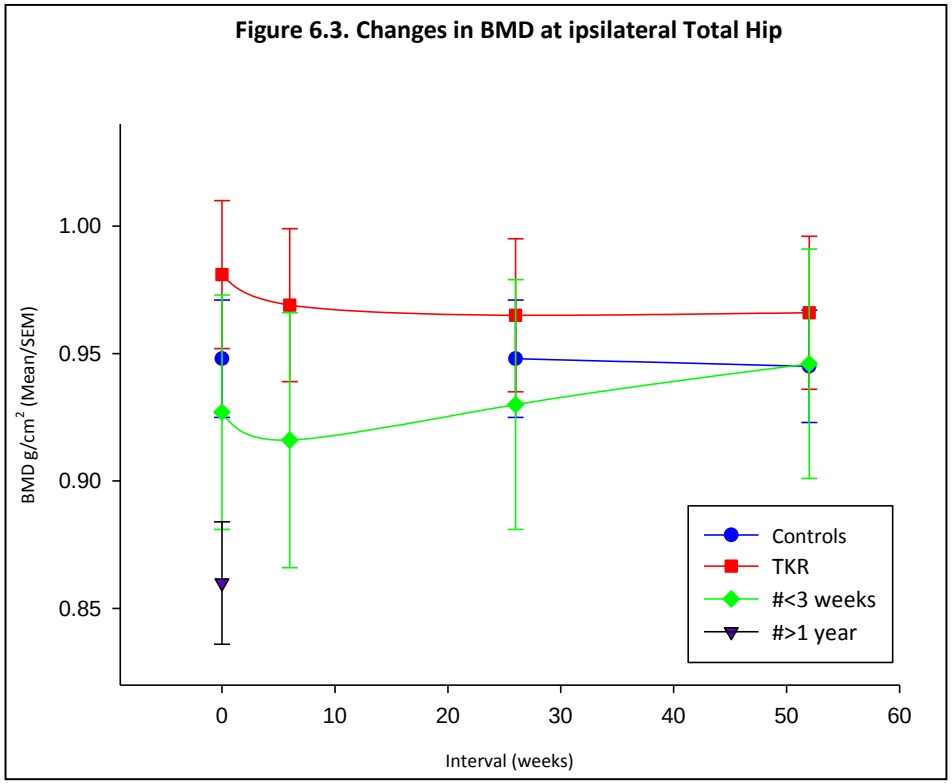


Figure 6.4. Changes in BMD at contralateral Total Hip

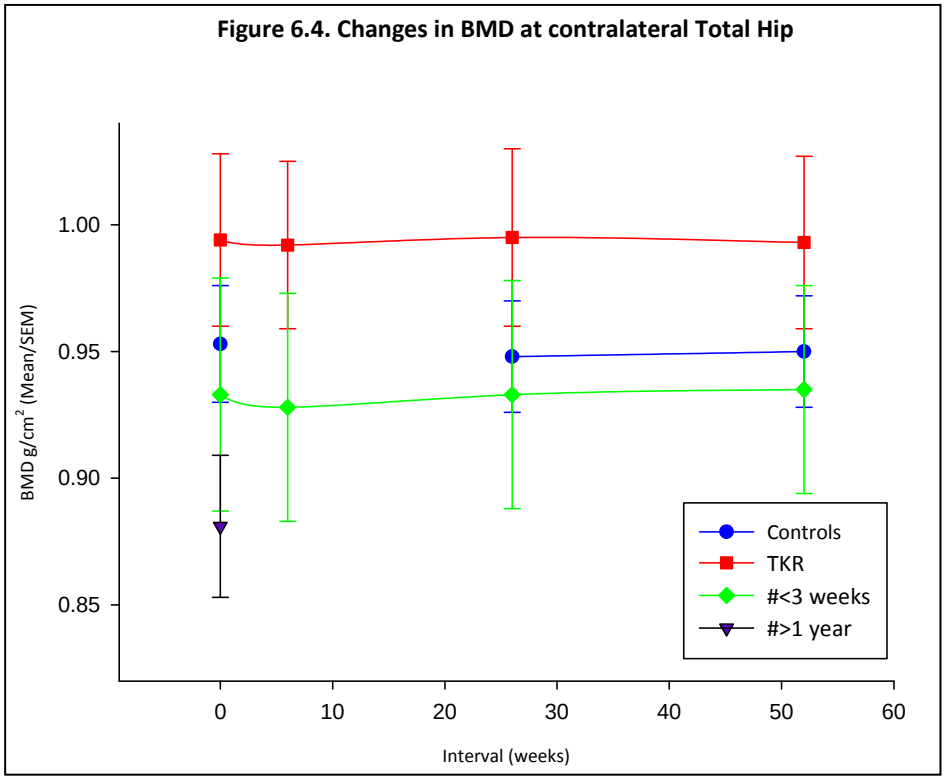


Figure 6.5. Changes in BMD at ipsilateral Greater Trochanter

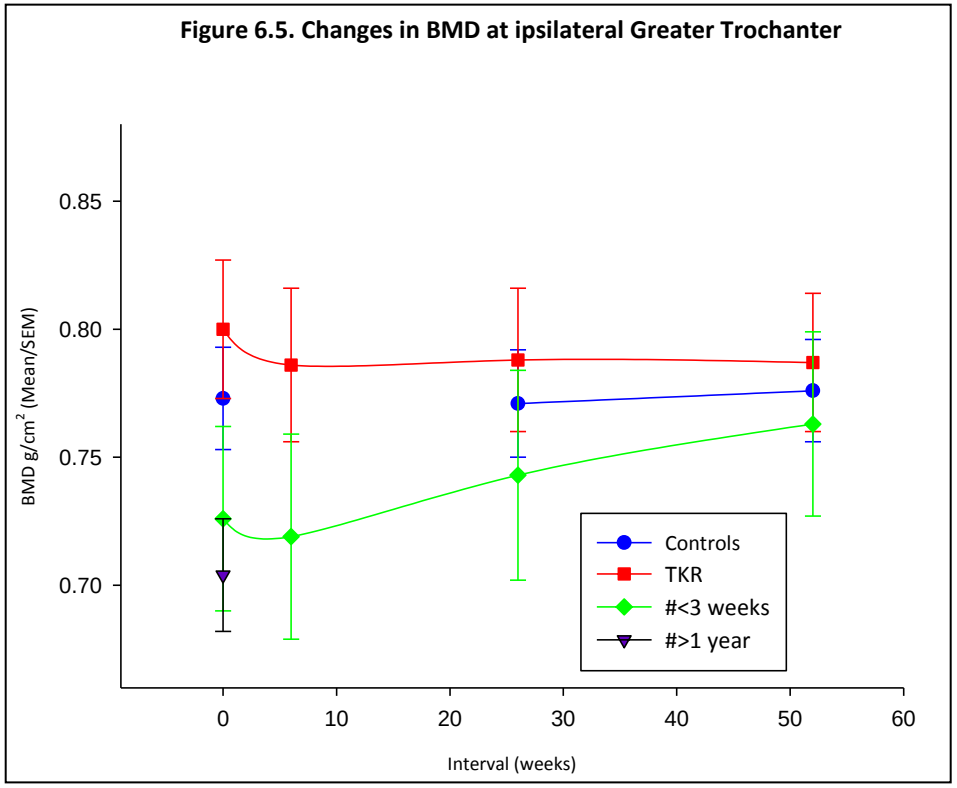


Figure 6.6. Changes in BMD at contralateral Greater Trochanter

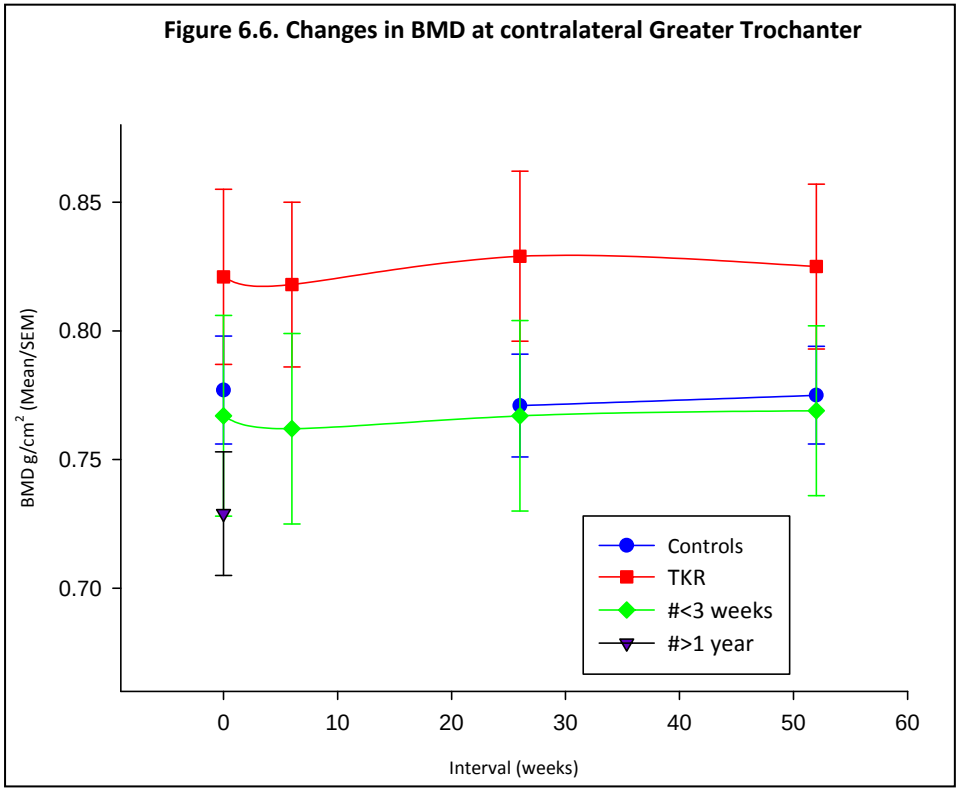


Figure 6.7. Changes in BMD at ipsilateral Femoral Shaft

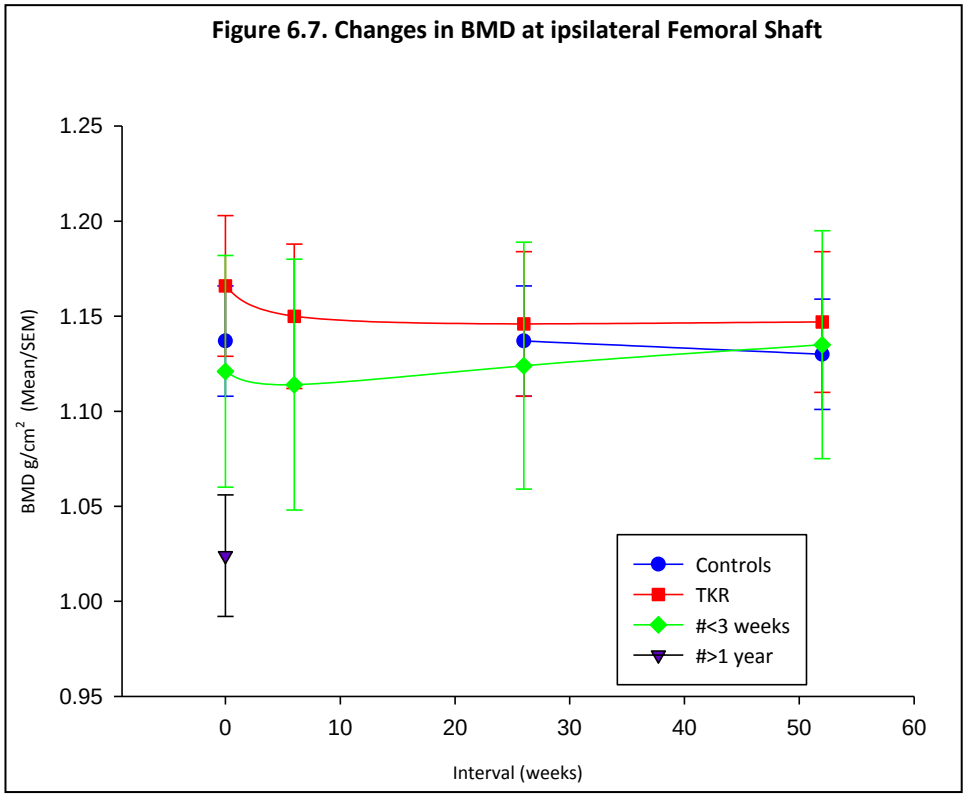


Figure 6.8. Changes in BMD at contralateral Femoral Shaft

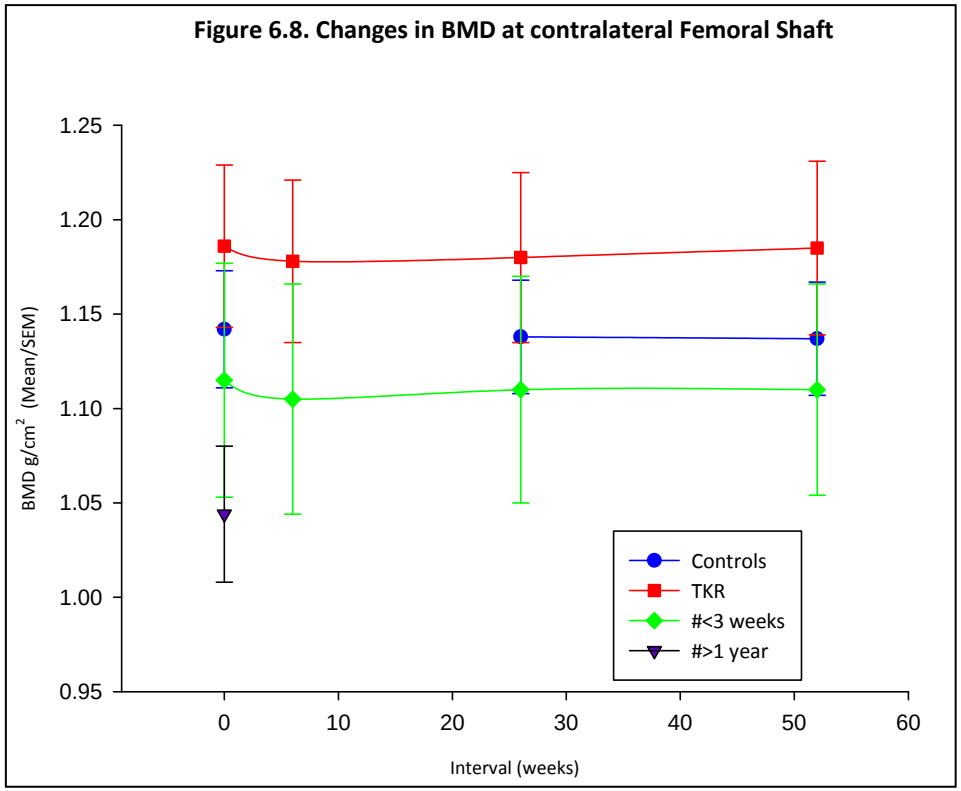


Figure 6.9. Changes in BMD at ipsilateral Wards Triangle

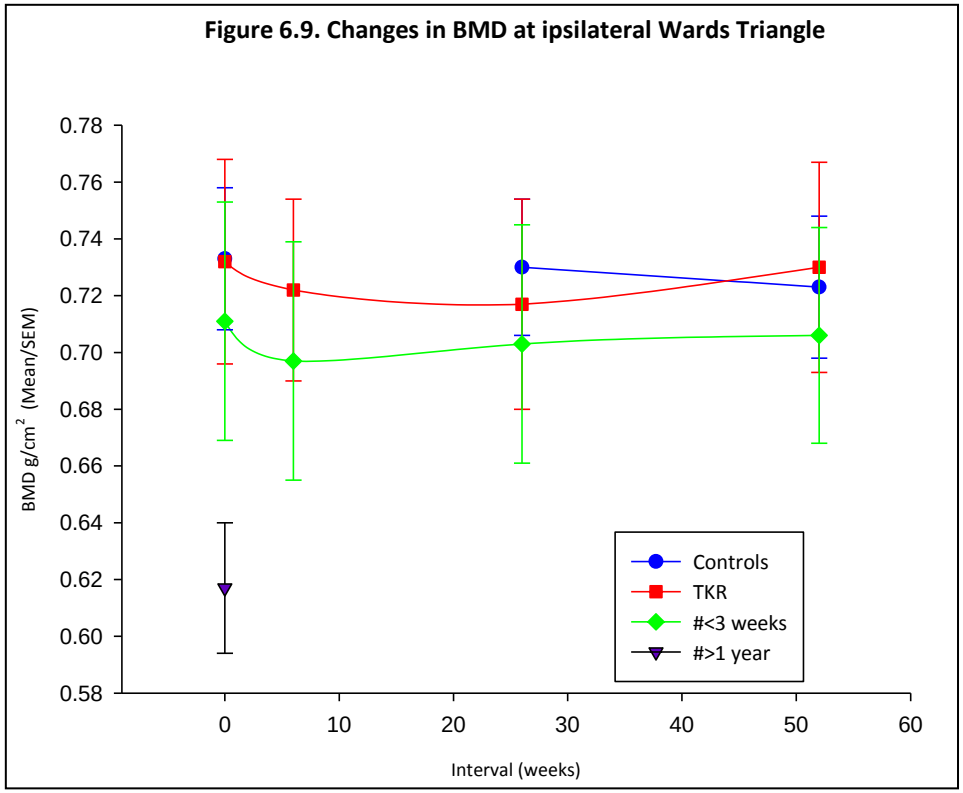


Figure 6.10. Changes in BMD at contralateral Wards Triangle

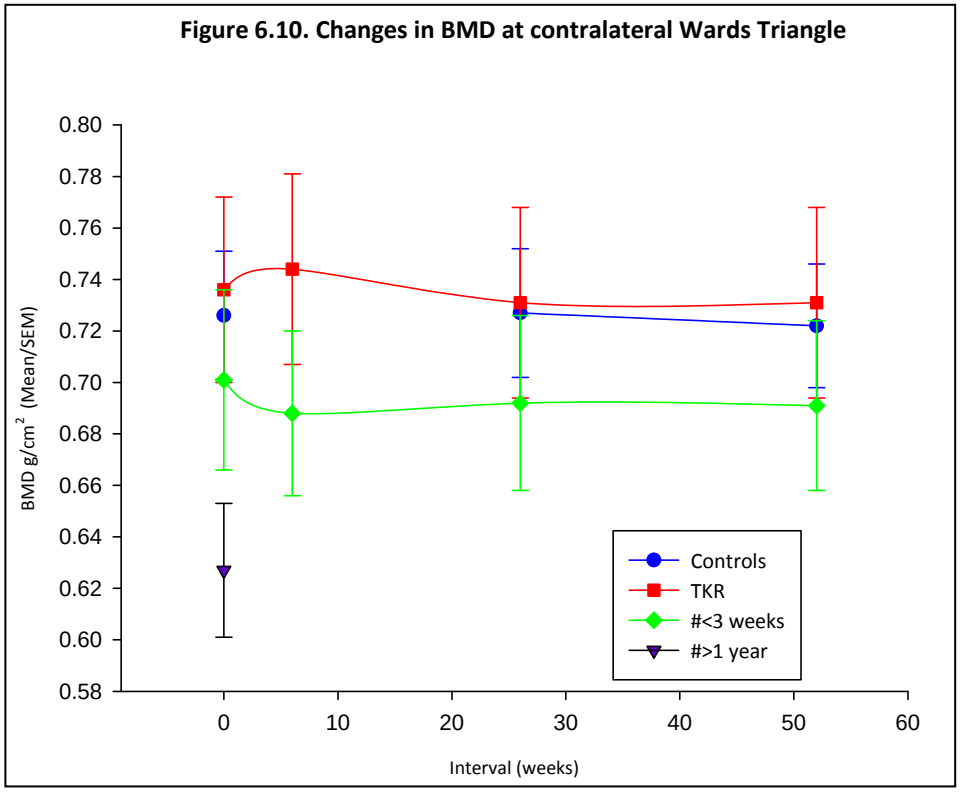


Figure 6.11. Changes in ipsilateral leg fat

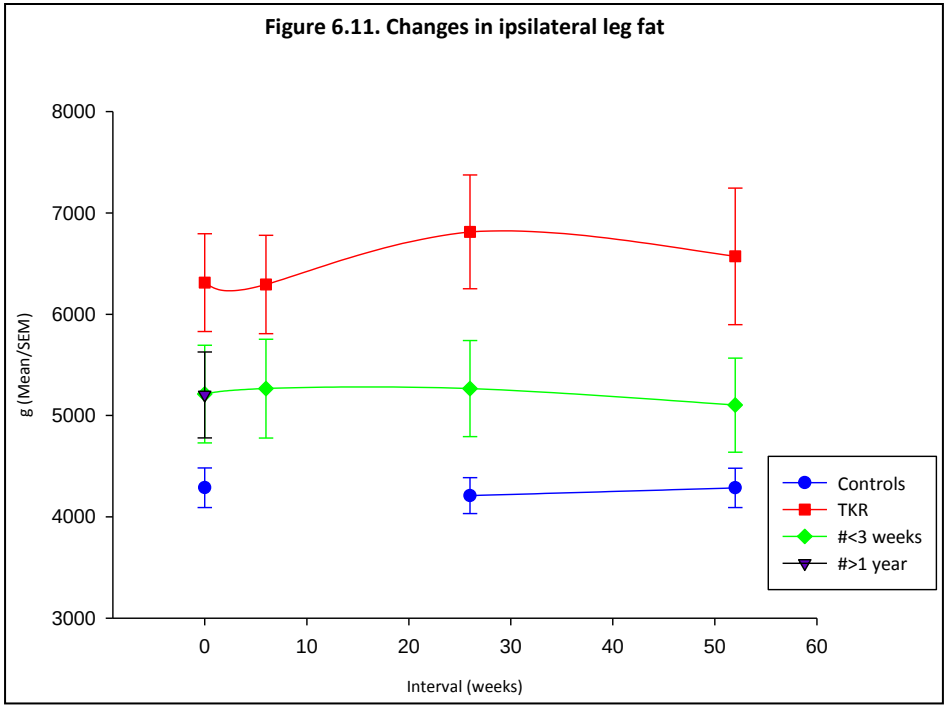
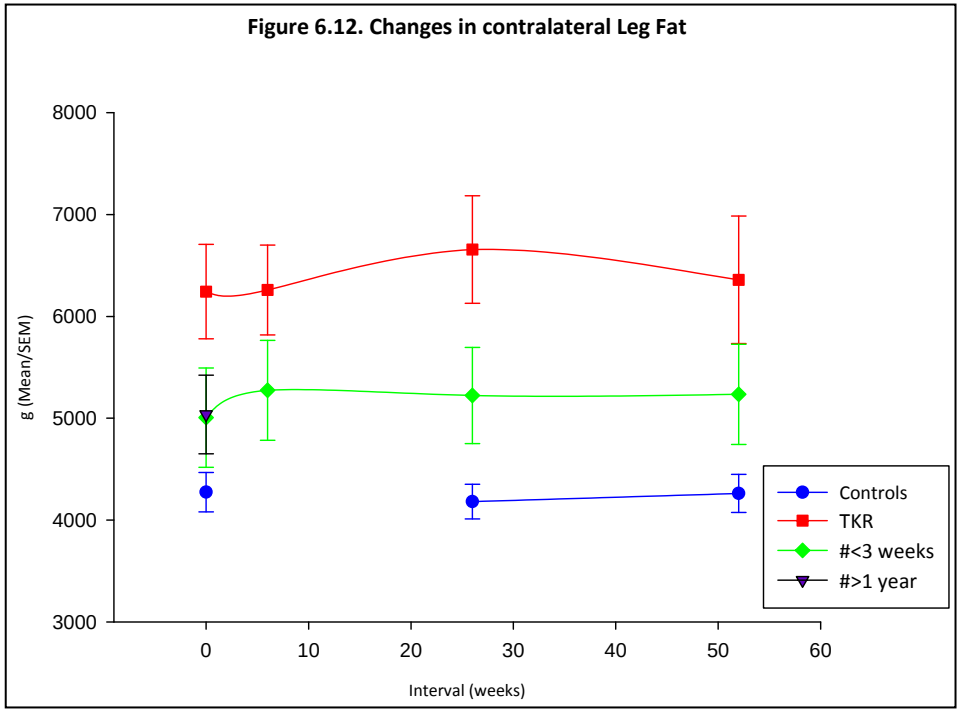


Figure 6.12. Changes in contralateral Leg Fat



Baseline data removed for #<3 weeks group wearing plaster cast

Figure 6.13. Changes in ipsilateral Leg Lean Tissue

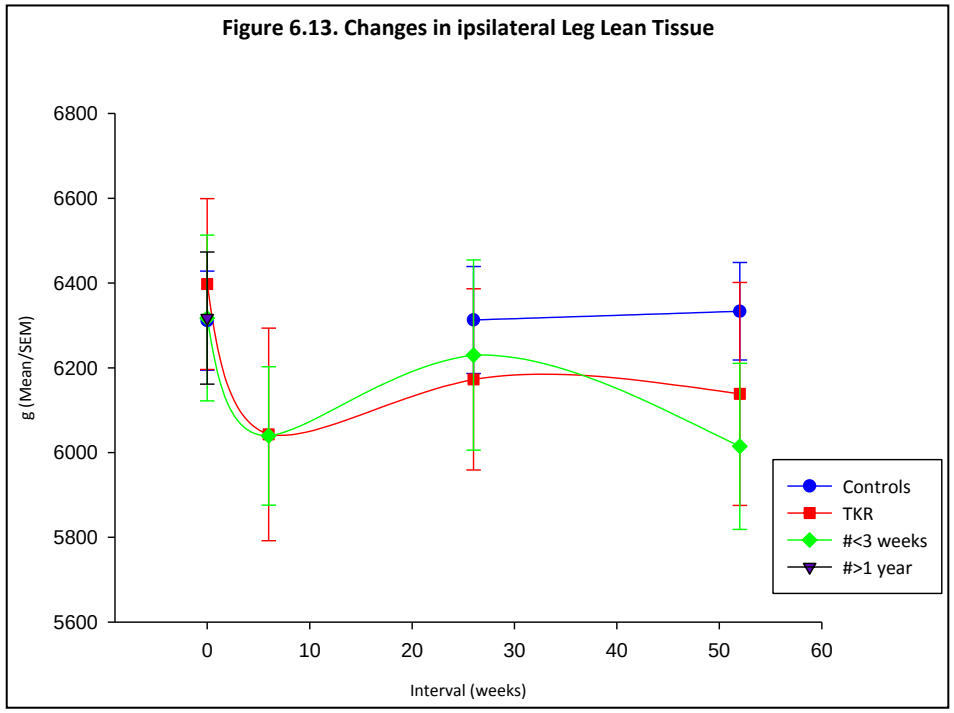
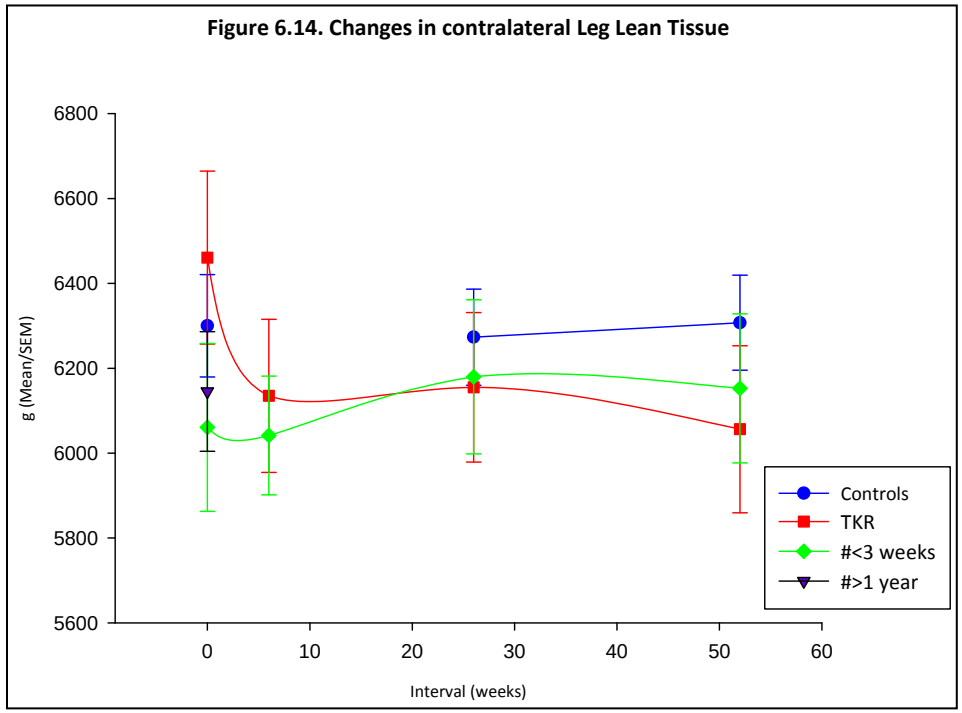


Figure 6.14. Changes in contralateral Leg Lean Tissue



Baseline data removed for #<3 weeks group wearing plaster cast

Figure 6.15. Changes in ipsilateral Hip Strength Index

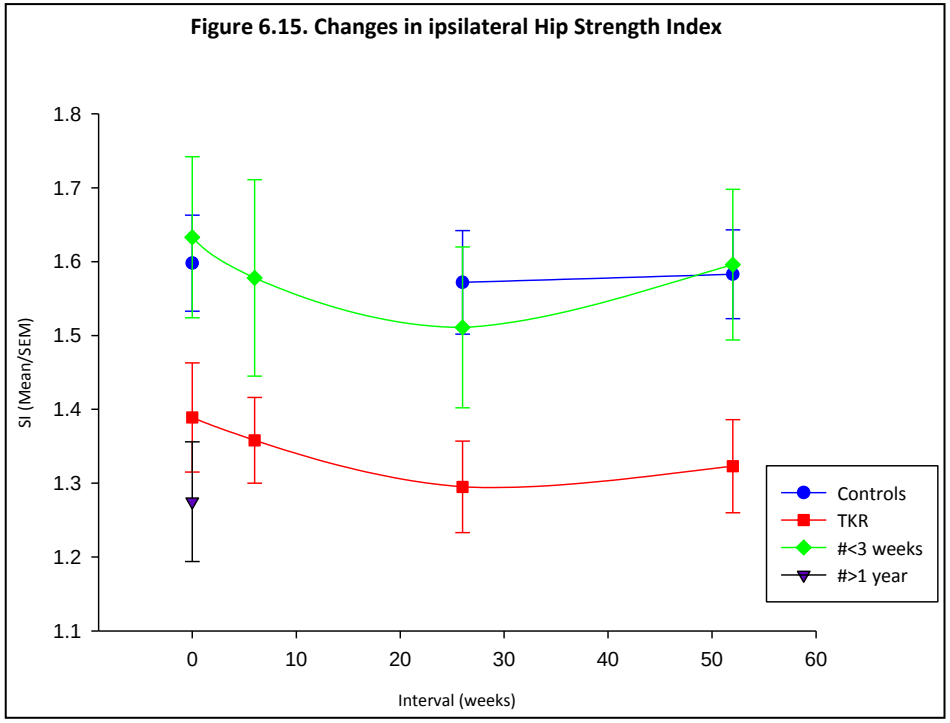


Figure 6.16. Changes in contralateral Hip Strength Index

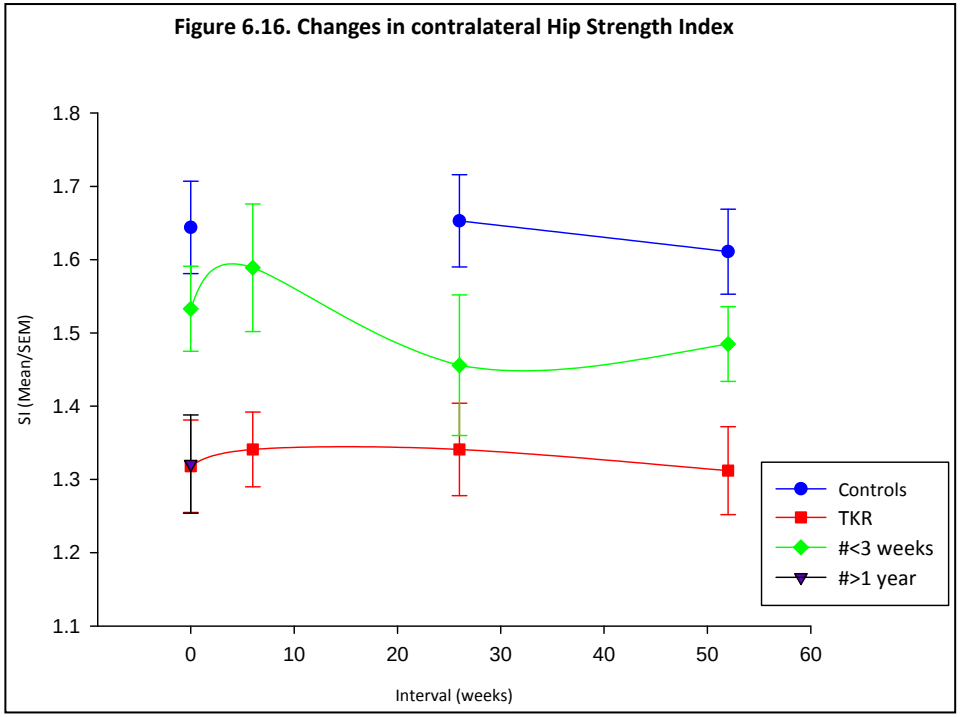


Figure 6.17. Changes in ipsilateral Hip Axis Length

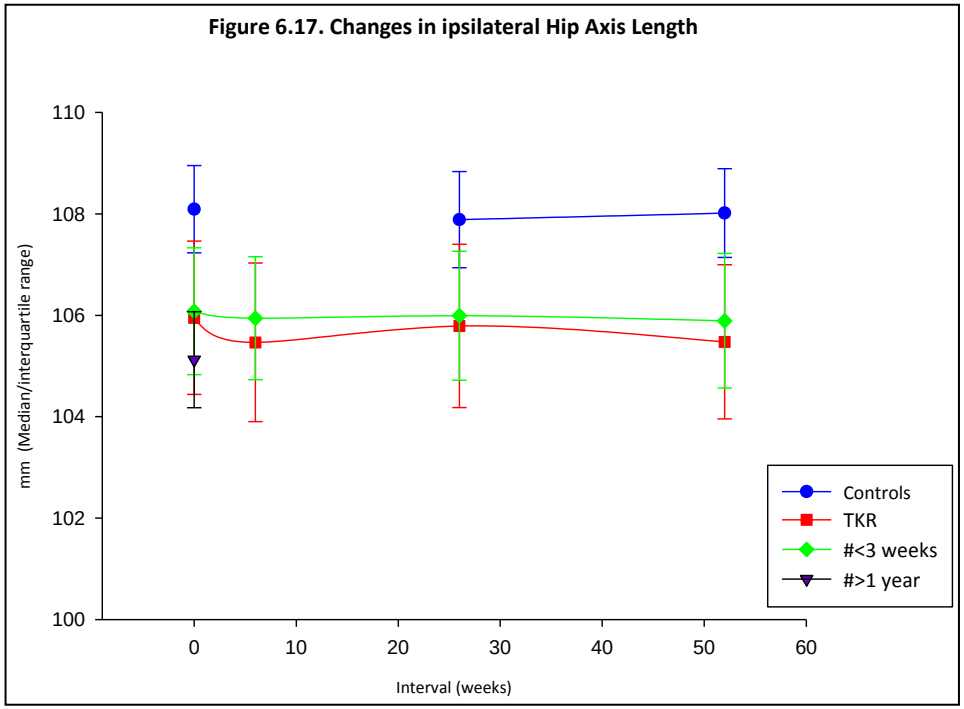


Figure 6.18. Changes in contralateral Hip Axis Length

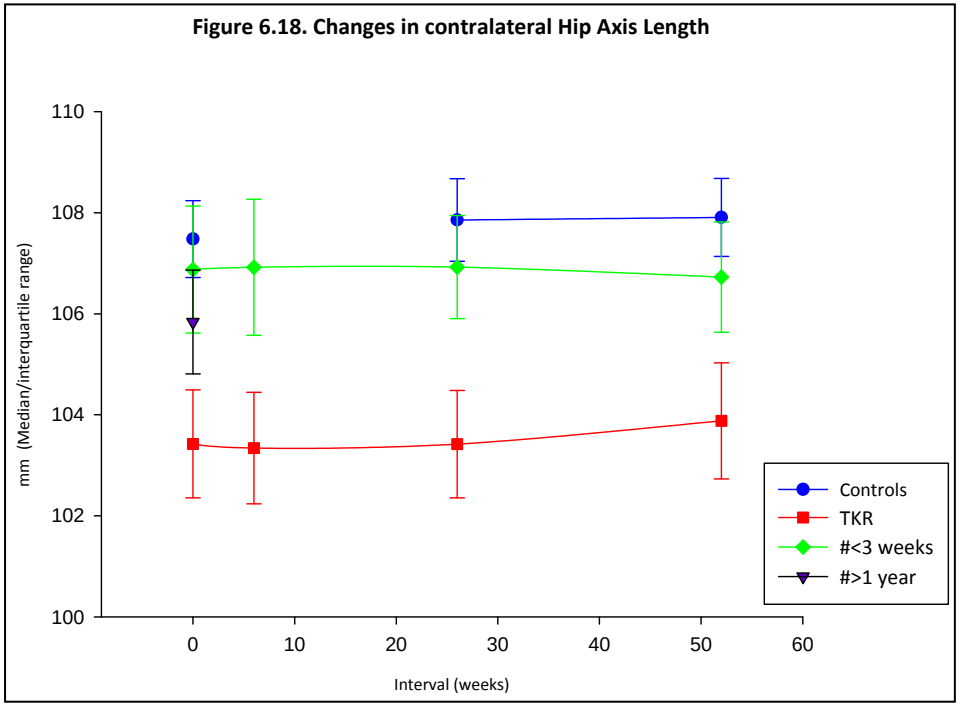


Figure 6.19. Changes in ipsilateral Hip CSMI

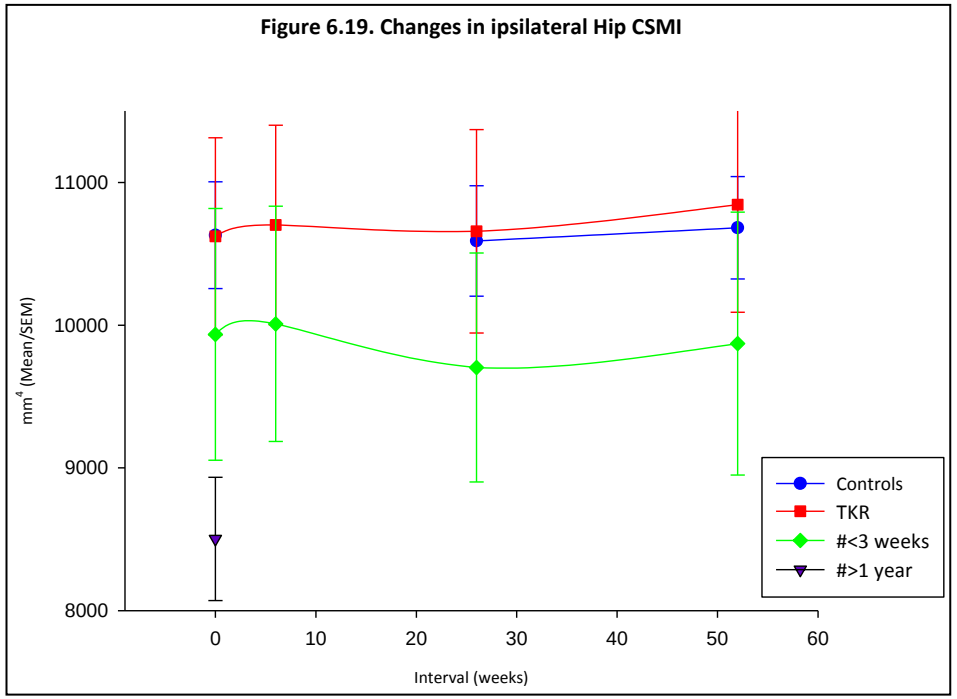


Figure 6.20. Changes in contralateral Hip CSMI

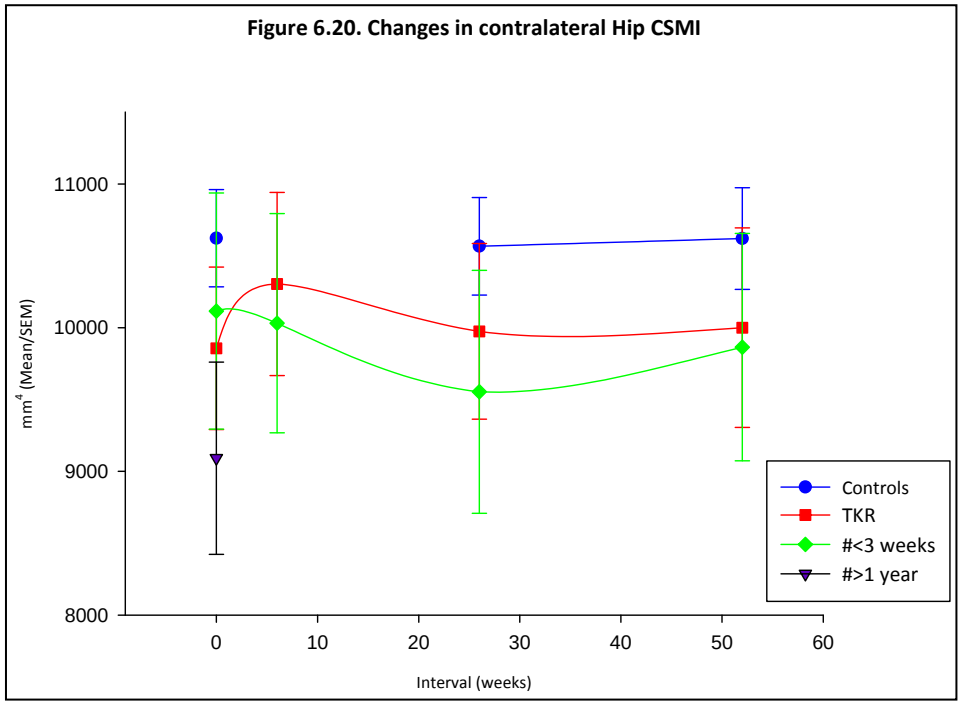


Figure 6.21. Changes in ipsilateral Hip CSA

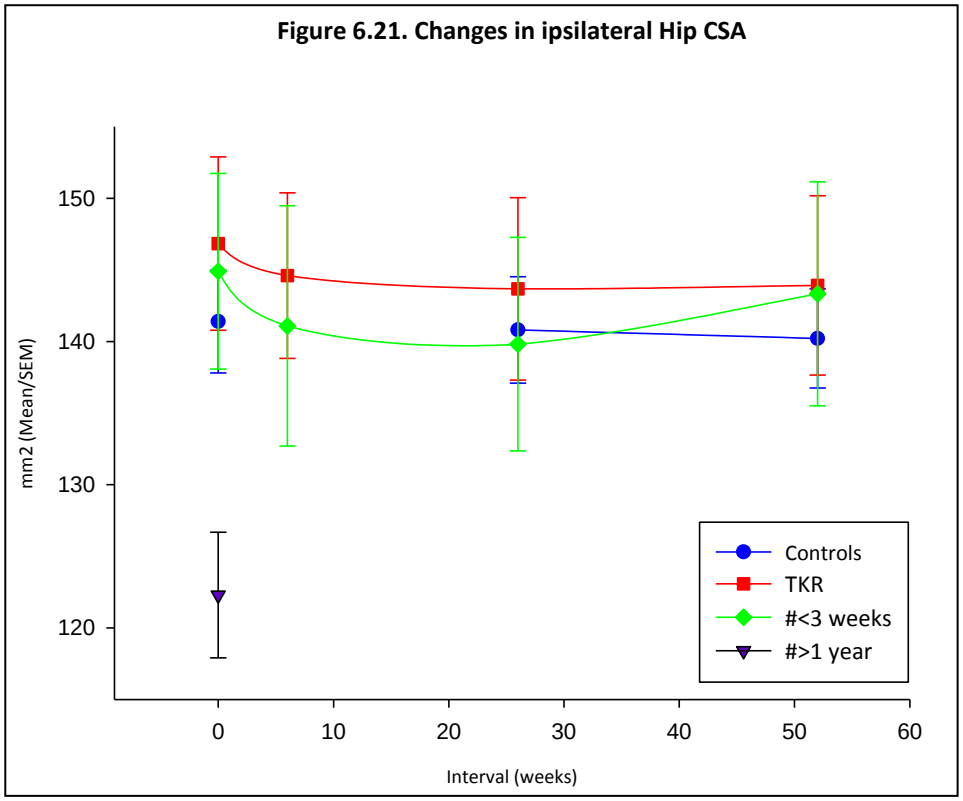
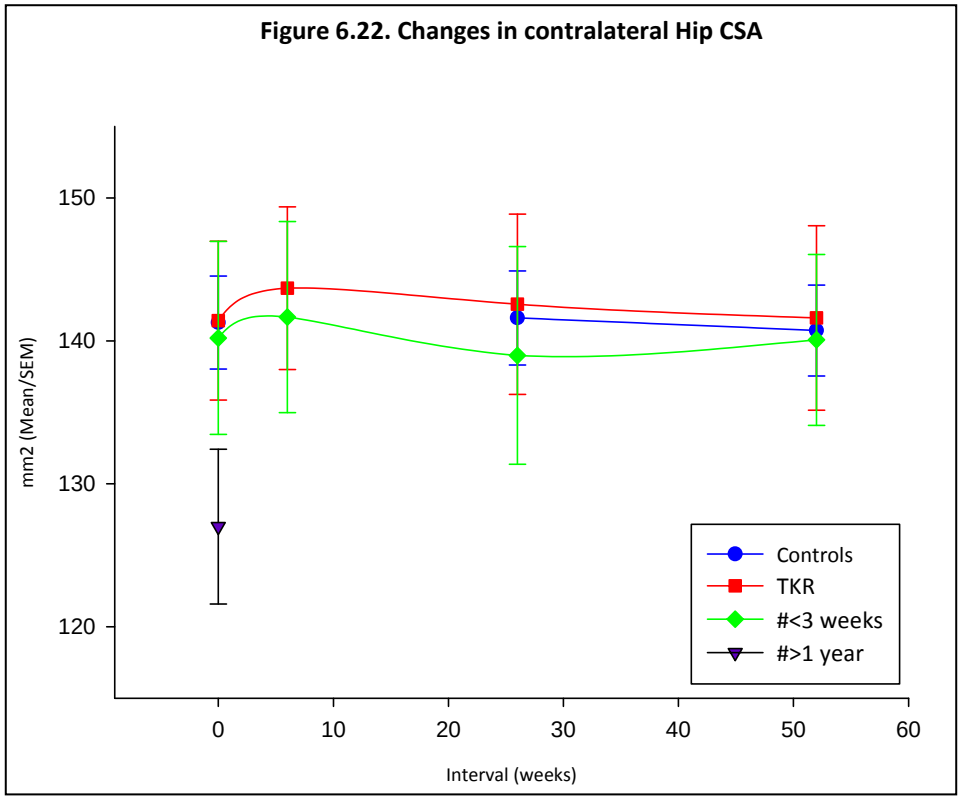


Figure 6.22. Changes in contralateral Hip CSA



The results reported in Table 6.1 give the longitudinal change in BMD at the ipsilateral NOF as both absolute values and as percentage change. Although the differences in group means are not statistically significant, means are not matched by the nature of the study design. As the mean is used as the denominator when calculating percentage change, differences in the means can result in a misleading impression of the equivalence of the percentage results i.e. an equal percentage change in BMD does not reflect an equal change in absolute BMD values nor does it reflect the increase in fracture risk due to bone loss. This effect is more clearly illustrated in Table 6.1 by applying a 10% BMD reduction to each group. This demonstrates that an equal percentage bone loss across the groups does not equate to BMD loss in absolute terms nor does it reflect the change in fracture risk as calculated by FRAX applied to the typical study participant aged 65 years, height 1.6m, weight 73kg, BMI 27.6 and no other risk factors (GE Lunar Prodigy).

Table 6.1. Change in BMD at Ipsilateral NOF over 4 visits expressed as absolute BMD and percentage change

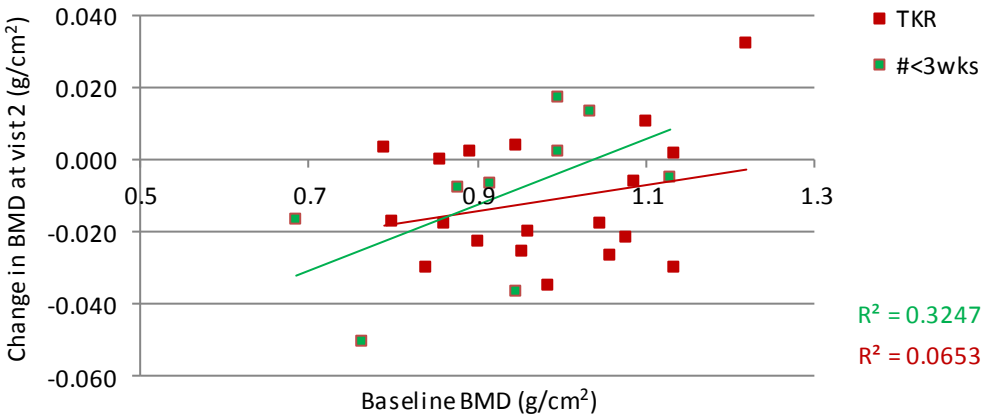
	Controls		TKR		#< 3wks	
	(g/cm2)	%	(g/cm2)	%	(g/cm2)	%
Baseline BMD at NOF (g/cm^2)	0.896	-	0.949	-	0.920	-
Change from baseline at 6 week visit	0.000	0.000	-0.007	-0.738	-0.011	-1.196
Change from baseline at 6 month visit	0.003	0.330	-0.013	-1.370	-0.017	-1.848
Change from baseline at 12 month visit	-0.008	-0.893	-0.016	-1.686	-0.005	-0.543
Change from baseline post 10% reduction	0.090	10.000	0.095	10.000	0.092	10.000
% Fracture risk - major osteoporotic fracture - at baseline*	-	7.0	-	6.5	-	6.7
% Fracture risk - major osteoporotic fracture -post 10% BMD reduction*	-	8.5	-	7.5	-	7..9
% Increase in fracture risk - major osteoporotic fracture -post 10% BMD reduction	-	21.4	-	15.4	-	17.9
% Hip fracture risk at baseline**	-	0.6	-	0.4	-	0.5
% Hip fracture risk post 10% BMD reduction**	-	1.2	-	0.8	-	1.0
% Increase in hip fracture riskpost 10% BMD reduction	-	100.0	-	100.0	-	100.0

* 10 year probability for major osteoporotic fracture calculated by FRAX based on a 65 year old female, Height 1.6m, Weight 73kg, BMI 27.56and no other risk factors (GE Lunar Prodigy)

**10 year probability for hip fracture calculated by FRAX based on a 65 year old female, Height 1.6m, Weight 73kg, BMI 27.6 and no other risk factors (GE Lunar Prodigy)

Figure 6.23 shows the correlation between ipsilateral total hip BMD at baseline, and the loss/gain in BMD at 6 weeks post baseline.

Figure 6.23. Relationship between baseline BMD and change in ipsilateral total hip BMD at visit 2



The following figures 6.24 and 6.25 depict changes in spine BMD L1-L4 and TBS measurements observed during the study period. Significances of differences between groups and of changes within groups over the study period are reported in Table 6.2.

Figure 6.24. Changes in BMD at Lumbar Spine L1-L4

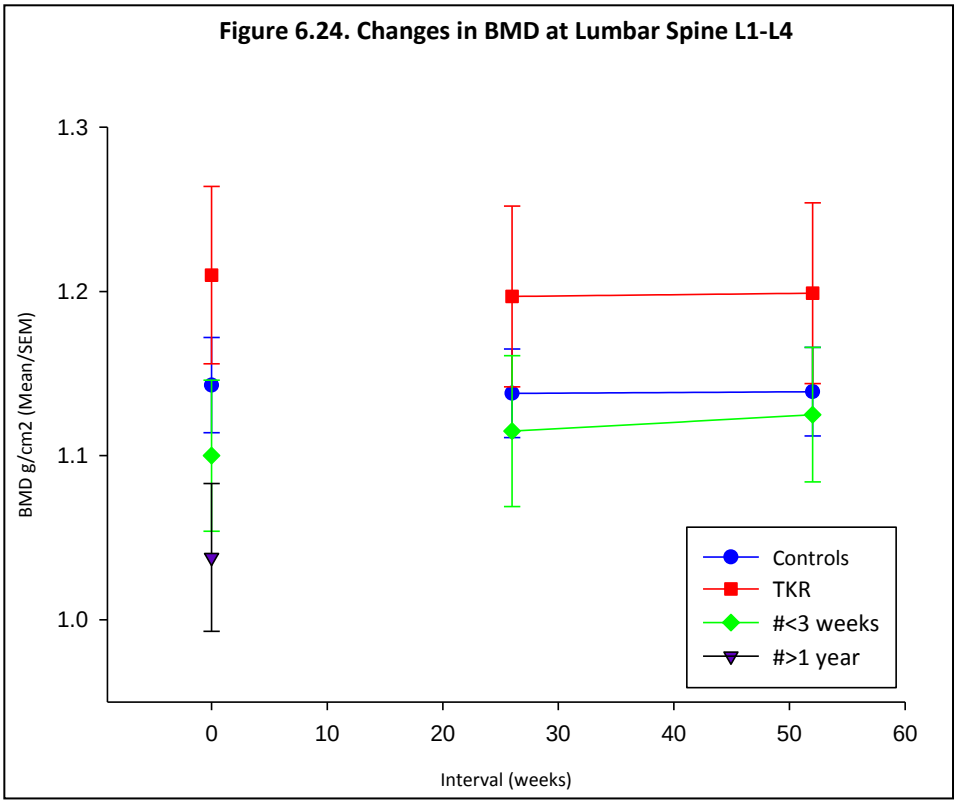
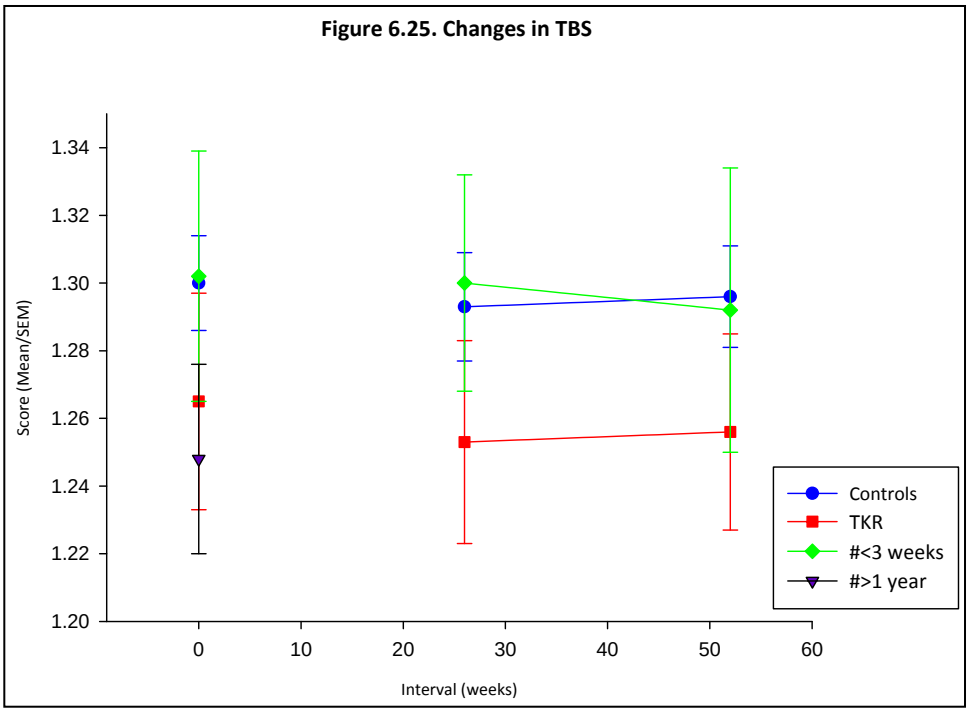


Figure 6.25. Changes in TBS



Although the overall measurements were higher for the TKR group and lower for the #<3weeks group, the baseline results for BMD at the hip and lumbar spine did not reveal any statistically significant differences compared to the controls. The results were however significant for the #>1year group who demonstrated lower BMD at all sites (p=<0.05), (ipsilateral Ward's triangle p=<0.01), with the notable exception of the contralateral total hip, greater trochanter and femoral shaft.

No significant changes occurred from baseline in bone or body composition parameters in the control group, except for a reduction in ipsilateral BMD at the NOF (p=<0.05) at visit 4 and a reduction in contralateral total hip BMD (p=<0.05) at visit 3. No significant changes occurred on the contralateral side, for any of the other groups, in any parameter of bone or body composition except for a significant increase in leg fat in the #<3weeks group (5274±1474g, p=<0.05) at visit 2, and a reduction in LLTM for the TKRs at visit 2. Significant changes were however observed for the TKR and #<3weeks groups in the ipsilateral leg and are shown in figures 6.1 to 6.22. The TKR group demonstrated the greatest number of significant changes. BMD at the ipsilateral NOF declined progressively from 0.949±0.126 g/cm^2 at baseline to 0.936±0.134 g/cm^2, (p=<0.05) at visit 3, remaining at that level at visit 4 (Fig.6.1). BMD at the ipsilateral total hip reduced rapidly from baseline 0.981±0.126 g/cm^2, to 0.969±0.132 g/cm^2, (p=<0.05) at visit 2, and further declined to 0.966±0.129 g/cm^2, (p=<0.05) at the final visit (Fig.6.3). A comparable pattern of bone loss was also demonstrated in the greater trochanter and femoral shaft (Figs. 6.5 and 6.7). In each case the BMD at the end of the study was significantly (p=<0.05) lower than at baseline. By contrast, the #<3weeks group sustained initial rapid losses from baseline (0.927±0.137 g/cm^2) in BMD at the ipsilateral total hip, to 0.916±0.151, (p=<0.05) at visit 2, but improved thereafter to a

level of 0.946±0.135, (n.s) at the end of the study, above the baseline measurement (Fig.6.3). Again, the same pattern was repeated for the greater trochanter with a highly significant improvement at visit 4 (0.763±0.109g/cm^2, p=<0.01) from baseline (0.726±0.107g/cm^2) (Fig.6.5). The improvement to above baseline at the end of the study, in this group, may possibly be accounted for by the delay after the initial injury in taking baseline measurements. The mean interval between injury and surgery was 20 days and as bone loss appears to be a very rapid response to immobilization, participants were likely to have already sustained some reduction in BMD by the time that they presented at the baseline visit. Measurements were higher for both the total hip and greater trochanter on the contralateral side (n.s compared to the ipsilateral side) and these contralateral measurements are probably indicative of the original ipsilateral BMD at the time of the injury.

The differences between mean ipsilateral and contralateral measurements at baseline were compared for all groups and all parameters. Significant differences were only revealed for the two fracture groups. The #<3weeks group appeared to have higher fat (5212±5006g, p=<0.05) and lean (6317±587g, p=<0.05) tissue mass in the ipsilateral leg but this is probably erroneous as participants were all wearing plaster casts at their baseline visit which would have affected the DXA tissue measurements at this visit. The #>1year group had lower ipsilateral total hip BMD (0.860±0.119g/cm^2, p=<0.05), greater trochanter BMD (0.724±0.107g/cm^2, p=<0.05), and higher fat tissue (5204±2083g, p=<0.05) and lean tissue (6313±6145g, p=<0.05) compared to the contralateral leg.

The results for TBS at the lumbar spine (Table 6.2) did not demonstrate any significant differences between the groups at baseline, and no significant changes occurred over the one year study period in either TBS or BMD for any of the groups. A disparity between TBS and

BMD measurements is evident in the TKR group (Figs. 6.24 and 6.25). Whilst TBS and lumbar spine BMD are broadly equivalent for the other groups at baseline, the TKRs have higher mean L1-L4 BMD compared to controls but lower TBS.

Table 6.2 Densitometry results - bone

	Controls				TKR				#<3wks				#>1yr			
	n	Mean	SD		n	Mean	SD		n	Mean	SD		n	Mean	SD	
(1) Mean TBS Spine	43	**1.300**	0.092		19	**1.265**	0.141		9	**1.302**	0.111		24	**1.248**	0.137	
(3) Mean TBS Spine	43	**1.293**	0.105		19	**1.253**	0.133		9	**1.3**	0.097		0			
(4) Mean TBS Spine	43	**1.296**	0.100		19	**1.256**	0.127		9	**1.292**	0.126		0			
1BMD L1-L4	43	**1.143**	0.192		19	**1.21**	0.233		9	**1.1**	0.137		24	**1.038**	0.220	*
2 BMD L1-L4	0				0				0				0			
3 BMD L1-L4	43	**1.138**	0.178		19	**1.197**	0.242		9	**1.115**	0.137		0			
4 BMD L1-L4	43	**1.139**	0.180		19	**1.199**	0.238		9	**1.125**	0.124		0			
1Ipsi Femur BMD NOF	43	**0.896**	0.133		19	**0.949**	0.126		9	**0.92**	0.119		24	**0.816**	0.105	*
2 Ipsi Femur BMD NOF	0				19	**0.942**	0.128		9	**0.909**	0.131		0			
3 Ipsi Femur BMD NOF	43	**0.899**	0.136		19	**0.936**	0.134	†	9	**0.903**	0.117		0			
4 Ipsi Femur BMD NOF	43	**0.888**	0.130	†	19	**0.933**	0.135		9	**0.915**	0.117		0			
1Contra Femur BMD NOF	43	**0.903**	0.126		17	**0.937**	0.140		9	**0.897**	0.119		24	**0.831**	0.135	*
2 Contra Femur BMD NOF	0				17	**0.942**	0.143		9	**0.896**	0.105		0			
3 Contra Femur BMD NOF	43	**0.899**	0.124		17	**0.933**	0.152		9	**0.897**	0.123		0			
4 Contra Femur BMD NOF	43	**0.899**	0.120		17	**0.931**	0.156		9	**0.9**	0.124		0			
1IpsiFemur BMD Total Hip	43	**0.948**	0.149		19	**0.981**	0.126		9	**0.927**	0.137		24	**0.86**	0.119	*
2 IpsiFemur BMD Total Hip	0				19	**0.969**	0.132	†	9	**0.916**	0.151	†	0			
3 IpsiFemur BMD Total Hip	43	**0.948**	0.150		19	**0.965**	0.131	††	9	**0.93**	0.146		0			
4 IpsiFemur BMD Total Hip	43	**0.945**	0.144		19	**0.966**	0.129	†	9	**0.946**	0.135		0			
1Contra Femur BMD Total Hip	43	**0.953**	0.151		17	**0.994**	0.148		9	**0.933**	0.139		24	**0.881**	0.136	
2Contra Femur BMD Total Hip	0				17	**0.991**	0.145		9	**0.928**	0.136		0			

3 Contra Femur BMD Total Hip	43	**0.948**	0.146	†	17	**0.995**	0.153		9	**0.933**	0.136		0			
4 Contra Femur BMD Total Hip	43	**0.950**	0.142		17	**0.993**	0.150		9	**0.935**	0.124		0			
1Ipsi Femur BMD Greater troch	43	**0.773**	0.134		19	**0.8**	0.119		9	**0.726**	0.107		24	**0.704**	0.107	*
2 Ipsi Femur BMD Greater troch	0				19	**0.786**	0.131	†	9	**0.719**	0.119		0			
3 Ipsi Femur BMD Greater troch	43	**0.771**	0.136		19	**0.788**	0.124	†	9	**0.743**	0.122		0			
4 Ipsi Femur BMD Greater troch	43	**0.776**	0.128		19	**0.787**	0.119	†	9	**0.763**	0.109	††	0			
1ContraFemur BMD Greater troch	43	**0.777**	0.135		17	**0.821**	0.146		9	**0.767**	0.116		24	**0.729**	0.116	
2 ContraFemur BMD Greater troch	0				17	**0.817**	0.139		9	**0.762**	0.111		0			
3 ContraFemur BMD Greater troch	43	**0.771**	0.129		17	**0.829**	0.142		9	**0.767**	0.111		0			
4 ContraFemur BMD Greater troch	43	**0.775**	0.124		17	**0.825**	0.138		9	**0.769**	0.098		0			
1Ipsi Femur BMD Wards	43	**0.733**	0.164		19	**0.732**	0.155		9	**0.711**	0.127		24	**0.617**	0.113	**
2 Ipsi Femur BMD Wards	0				19	**0.722**	0.137		9	**0.697**	0.125		0			
3 Ipsi Femur BMD Wards	43	**0.730**	0.160		19	**0.717**	0.159		9	**0.703**	0.125		0			
4 Ipsi Femur BMD Wards	43	**0.723**	0.163		19	**0.73**	0.162		9	**0.706**	0.115		0			
1Contra Femur BMD Wards	43	**0.726**	0.162		17	**0.736**	0.158		9	**0.701**	0.106		24	**0.627**	0.128	*
2 Contra Femur BMD Wards	0				17	**0.744**	0.163		9	**0.688**	0.097		0			
3 Contra Femur BMD Wards	43	**0.726**	0.161		17	**0.731**	0.160		9	**0.692**	0.100		0			
4 Contra Femur BMD Wards	43	**0.722**	0.155		17	**0.731**	0.162		9	**0.691**	0.098		0			
1IpsiFemur BMD Shaft	43	**1.137**	0.191		19	**1.166**	0.161		9	**1.121**	0.182		24	**1.024**	0.157	*
2 IpsiFemur BMD Shaft	0				19	**1.15**	0.166	†	9	**1.114**	0.199		0			
3 IpsiFemur BMD Shaft	43	**1.137**	0.189		19	**1.146**	0.167	†	9	**1.124**	0.194		0			
4 IpsiFemur BMD Shaft	43	**1.130**	0.188		19	**1.147**	0.161		9	**1.135**	0.180		0			
1Contra Femur BMD Shaft	43	**1.142**	0.204		17	**1.186**	0.189		9	**1.115**	0.186		24	**1.044**	0.178	
2 Contra Femur BMD Shaft	0				17	**1.178**	0.187		9	**1.105**	0.184		0			
3 Contra Femur BMD Shaft	43	**1.138**	0.200		17	**1.18**	0.196		9	**1.11**	0.181		0			
4 Contra Femur BMD Shaft	43	**1.137**	0.194		17	**1.185**	0.200		9	**1.11**	0.169		0			

1Total Body BMD Ipsi leg	43	**1.208**	0.127	19	**1.21**	0.139	9	**1.111**	0.074	*	24	**1.152**	0.139	
2 Total Body BMD Ipsi leg	0			19	**1.242**	0.150	9	**1.152**	0.115		0			
3 Total Body BMD Ipsi leg	43	**1.200**	0.128	19	**1.221**	0.146	9	**1.144**	0.119		0			
4 Total Body BMD Ipsi leg	43	**1.211**	0.127	19	**1.177**	0.177	9	**1.148**	0.115		0			
1Total Body BMD Contra Leg	43	**1.211**	0.131	19	**1.206**	0.124	9	**1.165**	0.089		24	**1.124**	0.125	*
2 Total Body BMD Contra Leg	0			19	**1.203**	0.124	9	**1.159**	0.091		0			
3 Total Body BMD Contra Leg	43	**1.205**	0.130	19	**1.199**	0.123	9	**1.165**	0.098		0			
4 Total Body BMD Contra Leg	43	**1.217**	0.130	18	**1.159**	0.166	9	**1.154**	0.088		0			

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

†p=<0.05 when compared to baseline for the same group

††p=<0.01 when compared to baseline for the same group

SD =standard deviation

Notes:

SD =standard deviation
BMD (g/cm^2)

Ipsi=ipsilateral, contra= contralateral

Table 6.3 Densitometry results - body composition and AHA

	Controls			TKR				#<3wks				#>1yr			
	n	Mean	SD	n	Mean	SD		n	Mean	SD		n	Mean	SD	
1Fat Android	43	2209	912	19	3544	1432	**	9	2628	966		24	2941	1325	*
2 Fat Android	0			19	3437	1546		9	2708	1054		0			
3 Fat Android	43	2220	940	19	3542	1577		9	2664	1038		0			
4 Fat Android	43	2263	930	19	3508	1798	**	9	2745	1013		0			
1Fat Gynoid	43	4652	1324	19	6058	1883	**	9	5254	1182		24	5426	1884	
2 Fat Gynoid	0			19	6096	2164		9	5367	1322		0			
3 Fat Gynoid	43	4591	1227	19	6273	2080	**	9	5353	1150		0			
4 Fat Gynoid	43	4628	1296	19	6057	2645	*	9	5392	1326		0			
1Lean Android	43	2809	291	19	3202	529	**	9	2825	373		24	2978	472	
2 Lean Android	0			19	3250	666		9	2840	325		0			
3 Lean Android	43	2838	297	19	3219	510	**	9	2900	361		0			
4 Lean Android	43	2845	303	19	3104	874		9	2922	402	†	0			
1Lean Gynoid	43	5682	620	19	5975	792		9	5693	714		24	5720	795	
2 Lean Gynoid	0			19	5872	861		9	5481	498		0			
3 Lean Gynoid	43	5727	621	19	5897	768		9	5649	614		0			
4 Lean Gynoid	43	5649	632	19	5707	1499		9	5616	574		0			
1Total Fat	43	24969	8249	19	36775	11661	**	9	28859	8267		24	30577	11731	*
2 Total Fat	0			19	36402	12169		9	29494	8415		0			
3 Total Fat	43	24911	7882	19	37950	12760	**	9	29038	8495		0			
4 Total Fat	43	25100	8193	19	36820	15183	**	9	29524	8488		0			

1Total Lean	43	39864	3455	19	42070	4922	*		9	38845	3073			24	39949	4207	
2 Total Lean	0			19	41427	5267			9	38360	2712			0			
3 Total Lean	43	39896	3613	19	41581	5128			9	39083	3167			0			
4 Total Lean	43	39810	3459	19	40357	8278			9	38880	3195			0			
1Fat Ipsi Leg	43	4287	1284	18	6313	2103	**		9	5212	1448			24	5204	2083	*
2 Fat Ipsi Leg	0			18	6294	2117			9	5266	1464			0			
3 Fat Ipsi Leg	43	4209	1161	18	6814	2447	**	†	9	5266	1424	*		0			
4 Fat Ipsi Leg	43	4286	1269	18	6572	2935	**		9	5103	1395			0			
1Fat Contra Leg	43	4274	1268	19	6244	2021	**		9	5006	1464			24	5037	1893	
2 Fat Contra Leg	0			19	6260	1923			9	5274	1474		†	0			
3 Fat Contra Leg	43	4181	1117	19	6658	2301	**		9	5223	1418	*		0			
4 Fat Contra Leg	43	4261	1229	19	6360	2727	**		9	5234	1478	*		0			
1Lean IpsiLeg	43	6311	766	18	6398	878			9	6317	587			24	6318	763	
2 Lean IpsiLeg	0			18	6043	1094		†	9	6039	490		†	0			
3 Lean IpsiLeg	43	6313	828	18	6173	933			9	6230	673			0			
4 Lean IpsiLeg	43	6334	755	18	6138	1148			9	6015	588			0			
1Lean Contra Leg	43	6300	791	19	6461	888			9	6061	594			24	6145	691	
2 Lean Contra Leg	0			19	6135	787		†	9	6041	420			0			
3 Lean Contra Leg	43	6273	743	19	6155	768			9	6180	545			0			
4 Lean Contra Leg	43	6307	734	19	6056	858			9	6153	528			0			
1Ipsi Femur CSMI	43	10630	2453	19	10622	3009			9	9936	2647			24	8503	2114	**
2 Ipsi Femur CSMI	0			19	10702	3046			9	10009	2473			0			
3 Ipsi Femur CSMI	43	10590	2535	19	10658	3105			9	9704	2406		†	0			
4 Ipsi Femur CSMI	43	10682	2353	19	10845	3287			9	9871	2764			0			
1Contra CSMI	43	10623	2217	17	9856	2464			9	10115	2465			24	9092	3279	*
2 Contra CSMI	0			17	10304	2778			9	10031	2289			0			

3 Contra CSMI	43	10567	2224	17	9974	2667		9	9553	2536		0			
4 Contra CSMI	43	10621	2320	17	10000	3026		9	9864	2374		0			
1Ipsi Femur SI	43	1.598	0.4	19	1.401	0.3		9	1.634	0.3		24	1.277	0.4	**
2 Ipsi Femur SI	0			19	1.36	0.3		9	1.584	0.4		0			
3 Ipsi Femur SI	43	1.573	0.5	19	1.304	0.3	*	9	1.519	0.3	†	0			
4 Ipsi Femur SI	43	1.583	0.4	19	1.323	0.3	*	9	1.596	0.3		0			
1Contra SI	43	1.644	0.4	17	1.33	0.3	**	9	1.529	0.2		24	1.317	0.3	**
2 Contra SI	0			17	1.348	0.2		9	1.586	0.3		0			
3 Contra SI	43	1.654	0.4	17	1.346	0.3	**	9	1.446	0.3		0			
4 Contra SI	43	1.611	0.4	17	1.312	0.3	**	9	1.485	0.2		0			

**p=<0.05 when compared to control group*

***p=<0.01 when compared to control group*

†p=<0.05 when compared to baseline for the same group

††p=<0.01 when compared to baseline for the same group

SD =standard deviation

Notes:

SD =standard deviation
Fat and lean (g)

Ipsi=ipsilateral, contra= contralateral

The results for body composition (Table 6.3) revealed highly significant differences (p=<0.01) between the TKR group and controls with much higher measurements of android, gynoid, ipsilateral & contralateral leg and total body fat, as expected given the high BMI (32.2±7.1, p=<0.01) of this group. There were no significant differences in this group for lean tissue measurements with the exception of higher levels of android lean tissue (3202±529g, p=<0.01). The body composition measurements for the #<3weeks group were not significantly different to the controls at baseline, although bilateral measurements of leg fat increased post injury and became significant at visit 3. Body composition for the #>1year group did not differ greatly from the controls except with regard to higher levels of android, ipsilateral leg and total body fat (p=<0.05) consistent with their higher BMI (28.4±5.5, p=<0.05).

Body composition changes were demonstrated in the TKR group with a significant increase in ipsilateral leg fat at visit 3 (6814±2447g, p=<0.05) which reduced again close to baseline level at visit 4 (6572±2935, n.s). Both ipsilateral and contralateral legs showed a marked and rapid reduction in LLTM at visit 2 (p=<0.05) with mean losses of 355±643g and 326±614g respectively. This muscle loss was not restored at visit 4 (Figs 6.13 and 6.14). The #<3weeks group appeared to lose LLTM only at the ipsilateral leg, with a mean reduction of 278±292g (p=<0.05) at visit 2, but this is possibly an anomaly resulting from the presence of plaster casts at the baseline visit.

The results for AHA (Table 6.3) demonstrate no significant differences at baseline between controls and the TKR group in measurements of ipsi- and contralateral CSMI, or ipsilateral SI but the contralateral SI is significantly lower (1.33±0.3, p=<0.01) compared to 1.64±0.4

for the controls. No significant differences exist between the #<3weeks group and controls but the #>1year demonstrate significant differences in all AHA parameters being lower than the controls in ipsilateral CSMI (8503±2114, p=<0.01), contralateral CSMI (9092±3279, p=<0.05), ipsilateral SI (1.28±0.4, p=<0.01) and contralateral SI (1.32±0.3, p=<0.01).

The only significant changes in AHA parameters were seen in the #<3weeks group who sustained a reduction in CSMI at visit 3 (9704±2406, p=<0.05) that improved again at visit 4 (Fig.6.19). A commensurate change in SI (Fig.6.15) was shown, as would be expected since the calculation of SI is derived from CSMI.

Table 6.4 Participants Z scores at baseline - visit 1

	Controls n=43	TKR n=19	#<3wks n=9	#>1yr n=24
BMD total hip - contralateral	0.66	0.66	0.34	0
BMD total hip - ipsilateral	0.62	0.5	0.27	-0.16
BMD spine L1-L4	0.96	1.16	0.41	-0.08

6.4.3 RELATIONSHIPS BETWEEN BONE & BODY COMPOSITION CHANGES AND FUNCTIONAL, PHYSICAL AND EMOTIONAL RECOVERY

Stepwise multiple regression analysis was performed to create a model of significant explanatory factors for changes in BMD at the ipsilateral total hip and changes in ipsilateral LLTM as dependent variables, at three time points during recovery, 6 weeks (visit2), 6 months (visit 3) and 1year (visit 4). These dependent variables were selected because they demonstrated the most significant changes during the study period and are potentially the greatest risk factors for future hip fracture and falls. As it was expected that there would be some delayed effect on bone loss resulting from the processes of recovery, the independent variables from the preceding visit (for which all appropriate data were available), for each time point of measures of the dependent variable, were used in the model. The resulting model summaries for each time point are shown in Tables 6.5 to 6.11 and reported below:

CHANGES IN BMD AT THE IPSILATERAL TOTAL HIP

The independent variables added into the model were:

Change in Ipsilateral LLTM

EQ5D Health state VAS

Prescribed calcium treatment

Bisphosphonate treatment

Ipsilateral weight-bearing

Pain VAS

Pedometer average steps per day

LEFS Score

Number of co-morbidities relating to bone health

Total of all co-morbidities

Physical therapy

Age

BMI

Number of knee replacements

PHQ9 Total score

GAD7 Total score

VISIT 2

Table 6.5. Model Summary: Dependent variable - Changes in BMD at the ipsilateral total hip at visit 2

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
TKR	1	.507[a]	.257	.204	.013011
#<3wks	1	.729[b]	.531	.464	.016164

a. Predictors: (Constant), LEFS Score 1

b. Predictors: (Constant), Pedometer Average visit 1

Controls: Not applicable.

TKR: Model 1 was a poor fit describing only 25.7% of variance in change in total hip BMD at visit 2 (R^2_{adj}= 20.4%), statistical significance $F_{1,14}$= 4.85, p=0.045. With other variables held constant, change in total hip BMD at visit 2 was negatively related to LEFS at visit 1, decreasing by 0.0005 g/cm^2 for every extra LEFS point (t= -2.20, p=0.045).

Change Ipsi Total Hip BMD = 0.00034 – 0.00050 LEFS (Eq.6.1)

#<3 weeks: Model 1 was an acceptable fit describing 53.1% of variance in change in total hip BMD at visit 2 (R^2_{adj}= 46.4%), statistical significance $F_{1,7}$= 7.92, p=0.026.

With other variables held constant, change in total hip BMD at visit 2 was negatively related to average number of daily pedometer steps at visit 1, decreasing by 0.00002 g/cm^2 for every extra step (t=-2.81, p=0.026).

Change Ipsi Total Hip BMD = 0.01909 - 0.0002 pedometer steps (Eq.6.2)

#>1yr: Not applicable.

VISIT 3

Table 6.6. Model Summary: Dependent variable - Changes in BMD at the ipsilateral total hip at visit 3

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
TKR	1	.502[a]	.252	.198	.020

a. Predictors: (Constant), Bisphosphonate1

Controls: No significant independent variables found.

TKR: Model 1 was a poor fit describing only 25.2% of variance in change in total hip BMD at visit 3 (R^2_{adj}= 19.8%), statistical significance $F_{1,14}$= 4.71, p=0.048. With other variables held constant, change in total hip BMD at visit 3 was positivelyrelated to bisphosphonate use at visit 1, increasing by 0.034g/cm^2 for bisphosphonate use (t= -2.20, p=0.045).

Change Ipsi Total Hip BMD = -0.019 + 0.34 bisphosphonate (Eq.6.3)

#<3 weeks: No significant independent variables found.

#>1yr: Not applicable.

VISIT 4

Table 6.6
7. Model Summary: Dependent variable - Changes in BMD at the ipsilateral total hip at visit 4

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
Controls	1	.447[a]	.200	.179	.015009
	2	.535[b]	.286	.249	.014358
TKR	1	.702[a]	.493	.461	.018788
#<3wks	1	.746[c]	.556	.493	.013804

a. Predictors: (Constant), Bisphosphonate3
b. Predictors: (Constant), Bisphosphonate3, Age
c. Predictors: (Constant), GAD-7 Total score 3

Controls: Model 2 was a poor fit describing only 28.6% of variance in change in total hip BMD at visit 4 (R^2_{adj}= 24.9%), statistical significance $F_{2,38}$= 7.62, p=0.002. With other variables held constant, change in total hip BMD at visit 4 was positively related to age and bisphosphonate use at visit 3, increasing by 0.001 g/cm^2 for every extra year in age (t= 2.12, p=0.038) and by 0.019 g/cm^2 for bisphosphonate use at visit 3 (t= 3.03, p=0.004).

Change Ipsi Total Hip BMD = -0.047 + 0.019 bisphosphonate + 0.001 age (Eq.6.4)

TKR: Model 1 was an acceptable describing 49.3% of variance in change in total hip BMD at visit 4 (R^2_{adj}= 46.1%), statistical significance $F_{1,16}$= 15.55, p=0.001. With other variables held constant, change in total hip BMD at visit 4 was positively related to bisphosphonate use at visit 3, increasing by 0.056 g/cm^2 for bisphosphonate use at visit 3 (t= 3.94, p=0.001).

Change Ipsi Total Hip BMD = -0.021 + 0.056 bisphosphonate (Eq.6.5)

#<3 weeks: Model 1 was an acceptable describing 55.6% of variance in change in total hip BMD at visit 4 (R^2_{adj}= 49.3%), statistical significance $F_{1,7}$= 8.775, p=0.021. With other variables held constant, change in total hip BMD at visit 4 was negatively related

to anxiety at visit 3, decreasing by 0.010 g/cm^2 for every extra GAD-7 point at visit 3 (t= 2.96, p=0.021).

$$\text{Change Ipsi Total Hip BMD} = 0.032 - 0.010 \text{ anxiety} \qquad \text{(Eq.6.6)}$$

#>1yr: Not applicable.

Table 6.8. Simplified summary of multiple regression analysis
Significant explanatory factors (from preceding visit) for change in BMD at the ipsilateral total hip

	Controls	TKR	#<3 wks	#>1yr
Visit 1				
Visit 2		↓ LEFS	↓ pedometer	
Visit 3		↑bisphosphonate use		
Visit 4	↑ age ↑ bisphosphonate use	↑ bisphosphonate use	↓ GAD-7 anxiety	

↑ Indicates mitigation of loss in BMD at the ipsilateral total hip as the score for the independent variable increases
↓ Indicates promotion of loss in BMD at the ipsilateral total hip as the score for the independent variable increases

CHANGES IN IPSILATERAL LLTM

The independent variables added into the model were:

EQ5D Health state VAS

Ipsilateral weight-bearing

Pain VAS

Pedometer average steps per day

LEFS Score

Total of all co-morbidities

Physical therapy

Age

BMI

Number of knee replacements

PHQ9 Total score

GAD7 Total score

VISIT 2

Controls: No significant independent variables found.

TKR: No significant independent variables found.

#<3 weeks: No significant independent variables found.

#>1yr: Not applicable.

VISIT 3

Table 6.9. Model Summary: Dependent variable - Changes in ipsilateral LLTM at visit 3

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
#<3wks	1	.726[a]	.526	.459	363.294

a. Predictors: (Constant), Pedometer Average visit 1

Controls: No significant independent variables found.

TKR: No significant independent variables found.

#<3 weeks: Model 1 was a good fit describing 52.6% of variance in change in ipsilateral LLTM at visit 3 (R^2_{adj}= 45.9%), statistical significance $F_{1,17}$= 7.78, p=0.027. With other variables held constant, change in LLTM at visit 3 was negatively related to average daily pedometer steps at visit 1, decreasing by 0.432g for every extra step (t= -2.79, p=0.027).

Change in ipsilateral LLTM = 568.144 – 0.432 pedometer steps (Eq.6.7)

#>1yr: Not applicable.

VISIT 4

Table 6.10. Model Summary: Dependent variable - Changes in ipsilateral LLTM at visit 4

Group	Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
TKR	1	.614[a]	.377	.338	749.291615
#<3wks	1	.689[b]	.474	.399	409.002181

a. Predictors: (Constant), Total all co-morbidities

b. Predictors: (Constant), Age Scan1

Controls: No significant independent variables found.

TKR: Model 1 was an acceptable fit describing 37.7% of variance in change in ipsilateral LLTM at visit 4 (R^2_{adj}= 33.8%), statistical significance $F_{1,16}$= 9.662, p=0.007. With other variables held constant, change in LLTM at visit 4 was positively related to the total number of co-morbidities, increasing by 421.72g for every extra co-morbidity (t= 3.11, p=0.007).

Change in ipsilateral LLTM = -13130.578 + 421.723 co-morbidities (Eq.6.8)

#<3 weeks: Model 1 was an acceptable fit describing 47.4% of variance in change in ipsilateral LLTM at visit 4 (R^2_{adj}= 39.9%), statistical significance $F_{1,7}$= 6.313, p=0.040. With other variables held constant, change in LLTM at visit 4 was negatively related to age, decreasing by 50.25g for every extra year (t=-2.51, p=0.040).

Change in ipsilateral LLTM = 2844.948 – 50.254 age (Eq.6.9)

#>1yr: Not applicable.

Table 6.11. Simplified summary of multiple regression analysis
Significant explanatory factors (from preceding visit) for change in ipsilateral LLTM

	Controls	TKR	#<3 wks	#>1yr
Visit 1				
Visit 2				
Visit 3			↓ pedometer	
Visit 4		↑ co-morbidities	↓ age	

↑ Indicates mitigation of loss in ipsilateral LLTM as the score for the independent variable increases
↓ Indicates promotion of loss in ipsilateral LLTM as the score for the independent variable increases

6.5 DISCUSSION

The consequences of immobilisation on bone and muscle loss are well known and have been reported in previous studies. Jarvinen and Kannus (11) provide a comprehensive review of studies, up to 1997, of injuries to the lower extremities and their effect on bone density. The studies are grouped into knee injuries, femoral shaft, tibial shaft and ankle fractures. It is evident from all of these studies that varying degrees of bone loss are associated with lower limb injury, including bone density changes in the contralateral limb. Several studies include measurement of BMD changes in the proximal femur/hip (6-9, 12, 187, 266). These studies, with one exception (8), showed long-term bone loss in the ipsilateral proximal femur/hip to a varying degree as a result of lower limb injury. The length of follow up period and the sample populations, in terms of age and sex, varied greatly in these studies. In each case the sample size was

very small, maximum 29 participants. No studies have emerged that specifically relate to bone loss at the hip in postmenopausal populations as a result of lower limb immobilization. Most studies were retrospective in design using bone density in the contralateral leg as a control. As bone loss may have occurred on both the ipsilateral and contralateral sides following injury, using the contralateral side as a control, without accounting for the possibility of a long-term residual bone deficit on that side, potentially underestimates the full extent of bone loss in the ipsilateral leg. To avoid these confounding effects, this study aimed to quantify these losses immediately following fracture or surgery and to compare these changes to an uninjured control group.

It is customary in the literature relating to bone densitometry to report longitudinal change as percentages rather than absolute figures alone. In order to calculate percentage change in any variable, the mean value of that variable for any given group is used as the denominator. Reporting percentage change is logical when comparing groups with matched means but, by the nature of this study, the means for the groups were not matched and there were, for example, distinct differences in baseline BMD at the NOF, although not statistically significant, as illustrated in Table 6.1. As the means, and therefore the denominators, for the groups were different, percentage change in BMD is not equivalent across the groups i.e. an equal reduction in BMD in percentage terms for the groups is not equivalent in either absolute terms nor in terms of increased fracture risk and change in percentage terms was not therefore reported for the remaining results.

The control group demonstrated consistency throughout the study and provided a meaningful contrast to the remaining groups. Although some age related bone loss was expected over the one year period in this postmenopausal population, apart from a reduction in ipsilateral/left-side BMD at the NOF at visit 4 and in the contralateral/right-side total hip BMD at visit 3, no significant changes occurred from baseline in either bone or body composition parameters. Age was nevertheless included in the multiple regression modelling as an explanatory variable to take account of its confounding effects on bone density.

Although the effects of immobilisation have been studied in a range of patient groups with varying pathologies, including spinal cord injury (176) and stroke (177-179), this has not been specifically studied in patients immediately following total knee replacement. The results (chapter 5) show that the TKR participants had a protracted period of reduced exercise and activity prior to surgery, with lower levels of daily exercise compared to all of the other groups. Given this functional impairment prior to surgery, and the fact that patients are encouraged to remobilize very quickly following their operation, it may have been reasonably expected that their knee replacement would afford a relatively rapid improvement in their condition and not greatly reduce their mobility and weight-bearing. Results from this study have demonstrated that this is not the case, and recovery in all areas of physical and functional parameters was slow and incomplete one year after surgery. Although they did not demonstrate the extremes of mechanical unloading on their ipsilateral leg shown by the fracture patients (having mean ipsilateral weight-bearing of 43.8±6.3 % at 6 weeks after surgery), TKR patients returned to full function and activity much more slowly, resulting in significant ipsilateral bone loss at the hip with bilateral muscle atrophy. This study employed a

recently developed software tool, Trabecular Bone Score, which is designed to evaluate bone microarchitecture at the lumbar spine from grey-level pixel variations in the raw DXA image data (267). An interesting disparity was revealed between TBS and BMD measurements in the TKR group (Figs. 6.24 and 6.25). Whilst TBS and lumbar spine BMD are broadly equivalent for the other groups at baseline, TKRs have higher mean L1-L4 BMD compared to controls but lower TBS. Previous research on bone affected by osteoarthritis has suggested that the higher bone mass associated with OA is protective against fracture and that the conditions of OA and osteoporosis are mutually exclusive (198, 199). Arden et al report evidence from large population studies where levels of BMD are up to 15% higher in OA patients compared to controls (203). A study by van Hove et al, investigating osteocyte morphology in human tibial bone from different pathological states, observed significant differences in OA and OP affected bone suggesting that the two conditions are quite distinct (53). More recent research indicates that the relationship between OA and OP is more complex than originally proposed (200). Glowacki (199) reports that several studies using DXA assessed BMD, demonstrate an incidence of occult OP in 20-29% of both men and women with OA. A study by Drees et al (201) found that in 82 osteoarthritic, postmenopausal females, (who subsequently required knee or hip replacement), 23.2% were affected by OP reflecting the normal distribution of OP in the general female population. Kumarasinghe et al (268) observed an altered state of trabecular bone remodelling and microarchitecture in primary hip OA. These studies suggest that, although higher BMD is part of the pathogenesis of OA, this potentially disguises poorer quality of sclerotic bone and inferior fracture resistance. Whilst some caution should be used in interpreting the results from TBS, as this software has not been fully validated for clinical use (267), the disparity between BMD and TBS in the TKR group is an interesting phenomenon that

supports the possibility that the relatively high BMD associated with OA potentially disguises poorer bone quality reflected by bone structural parameters. As increased BMD is generally associated with reduced fracture risk it might also be expected that OA patients would demonstrate reduced fracture prevalence. A number of studies however indicate that this is not the case (203-206). The reasons for this increased fracture risk are not clear but may be attributable to a variety of functional impairments associated with OA that possibly contribute to an increased propensity for falls and greater severity of injuries. These include reduced agility, reduced muscle strength, postural instability and heightened pain levels (203, 207). A study by Prieto-Alhambra et al (210) showed that patients with knee OA, from the General Practice Research Database (UK), have a non-significantly lower hip fracture incidence than controls in the year preceding total knee replacement (TKR), but a significantly increased hip fracture incidence in the year following surgery (RR 1.58; 95% CI) that only returns to the same level as the control group 3 years post-operatively. These results were supported by a further study using the Dutch PHARMO Record Linkage System (211). Whilst possible reasons for this phenomenon (propensity for falls etc.) are discussed, the extent of disuse-related bone loss at the hip following TKR and its potential contribution to post-surgical hip fracture risk has not been reported. Bone loss at the tibial and femoral diaphyses has been previously demonstrated following TKR and this was most marked in the operated leg for one year post-operatively (212). Post-surgical bisphosphonate use (BPU) has been found to be associated with a 50-55% hip fracture risk reduction in a TKR population (213). As BPU would be expected to alleviate the effects of disuse-related bone loss, this finding supports the hypothesis that the post-surgical disuse found in the TKR patients in this study, may play an important contributory role in hip fracture following TKR (214). Obesity in this TKR group is an

additional factor that could influence fracture risk. Obesity has not been generally considered as a risk factor for bone fracture as high BMI has generally been associated with higher BMD and it has also been suggested that fat tissue has a protective function in postmenopausal women by increasing remodelling associated with weight-bearing and possibly by cushioning against falls (161). The effects of obesity on bone are potentially complex as it is associated with altered hormone levels including higher serum concentrations of human parathyroid hormone (hPTH) and lower circulating 25-hydroxy-vitamin D both of which influence bone maintenance and quality (162). In terms of mechanical risk, applied loads during activity can create resultant forces many times greater than during normal stance and excessive stresses can be placed on bones, particularly during high impact activities (27). The adequacy of bones to support the greater loads to which they are subjected in obese people is becoming an area of increasing interest (161, 162). Skeletal alignment in obese people may also be a factor in increasing fracture risk. Alignment of the lower limb bones and joints can be substantially altered by increased soft tissue mass between the legs that compromises normal stance and gait (163). The altered efficiency of load distribution throughout the leg may potentially contribute to fracture risk. This may be further exacerbated by alterations in gait due to knee pain in OA sufferers with consequent instability and heightened risk for falling (261). Despite these complications, a study by Prieto-Alambra et al (269) found that the association between obesity and fracture in postmenopausal women was site-dependent and that obesity had a protective effect against hip fracture, possibly related to a padding effect of larger volume of soft tissue in the hip region.

The newly fractured group demonstrated relatively minimal changes over the study period, in any parameters of bone or body composition compared to the TKR group and, after an initial and statistically significant decline in BMD at the total hip, demonstrated good recovery in both physical and functional parameters over the one year period. By the end of the study they had returned to BMD levels comparable to the controls in all hip ROIs. In the case of the ipsilateral total hip and greater trochanter, there appears to be an improvement in BMD at the end of the study, to above the baseline level. This may possibly be accounted for by the delay after the initial injury in taking baseline measurements. The mean interval between injury and surgery was 20 days & and as bone loss appears to be a very rapid response to immobilization, participants were likely to have already sustained some reduction in BMD by the time that they presented at the baseline visit. Although the results for the #<3weeks group indicate a significant loss in ipsilateral muscle mass immediately following fracture, this may be due to the presence of plaster casts at the baseline visit causing erroneous DXA measurement of the lean leg tissue. Whilst there were bilateral fluctuations in LLTM in this group over the study period, they were not significant and the #<3weeks group completed the study with ipsilateral LLTM comparable to their contralateral leg at baseline. Nevertheless, it is notable that this group has lower muscle mass and higher leg fat bilaterally at all stages of the study compared to the controls. The only significant changes in AHA parameters were seen in the #<3weeks group who sustained a significant ($p=<0.05$) reduction in CSMI at visit 3 that improved again at visit 4 (Fig.6.19). It is not clear whether this has any relevance particularly as it was a very temporary change and is most probably due to the relatively high AHA precision errors, reported in chapter 2, table 2.5, which can arise from patient positioning differences between scans. Following the initial decline, the #<3weeks group present a picture of

good levels of recovery in all physical and functional parameters, but these findings were not supported by the results for the cross-sectional group who scored significantly below the control group in almost all key outcomes. The reasons for these contradictory results are not readily explained. It may be that the small sample available for the #<3weeks group has given misleading results or that the two fracture groups were not representative of comparable populations at the time their fractures occurred. Other than having lower muscle mass and higher leg fat bilaterally, the #<3weeks group did not demonstrate any significant differences from the controls and it is possible therefore that the #<3weeks group did not represent any difference in terms of fracture risk from their age-matched peers. Indeed the Z scores (Table 6.4) for the #<3weeks group were 0.34 and 0.27 for the contralateral & ipsilateral total hip, and 0.41 for the lumbar spine. As Z scores of zero would be representative of the average subject in the NHANES database, on which DXA diagnostics are based, this tends to suggest that the newly fractured group was not at any heightened risk for fracture on the basis of their BMD. For both fracture groups, the majority of injuries occurred at the ankle. Ankle fractures are not generally regarded as osteoporotic fractures (270) therefore it is consistent with this assertion that the occurrence of ankle fractures in the #<3weeks group is unrelated to low BMD. Z scores for the #>1yr group were 0, -0.16 and -0.08, i.e. below the level of age-matched peers on the NHANES database, except for the contralateral total hip. As their bone density status was not known at the time of their fracture, it is not possible to state whether they were at increased risk of fragility fracture at the time of their injury, although many were put onto bisphosphonate &/or calcium treatment shortly after their injury. It is notable however that the #>1yr group did not have significantly lower BMD at their contralateral total hip, greater trochanter and femoral shaft compared to controls suggesting that at the time of injury, their hip BMD was comparable to the control

group and the deficit in BMD on the ipsilateral side is the long-term consequence of the fracture and an impairment in general levels of function and activity post injury. Given that the #<3weeks group returned to normal levels of function and activity at the end of the study, it is unclear why these impairments in function and activity should be evident in the #>1yr group. As discussed in chapter 5, it is feasible that selection bias has influenced the results for the #<3weeks group and, due to their interest in the research topic, they may have been susceptible to the Hawthorne effect, modifying their behaviour to optimize their recovery. The outcomes for the #>1year group may therefore be more representative of patients sustaining leg fractures than the #<3weeks group. Regardless of whether or not the original injury for the #>1yr group was due to bone fragility, the study results show a long-term impairment in function, activity that may have contributed to an ipsilateral deficit in bone mass at the hip and reduced bilateral muscle mass compared to controls, which may predispose them to increased hip fracture risk in the future.

Relationships between bone & body composition changes and functional, physical and emotional recovery:

The most significant and important changes, in terms of potential fracture risk, that occurred during the study were reductions in BMD at the total hip and in bilateral LLTM. The explanatory factors for these dependent variables were assessed using multiple regression analysis and the results are summarised in tables 6.8 and 6.11. The models, explaining variation in total hip BMD change, produced a mixed picture for the different groups with some results contradicting expectations. Bisphosphonate use predicted mitigation of bone loss for the controls at visit 4 and for the TKRs at visit 3 and 4. Anxiety predicted bone loss at visit 4 for the #<3weeks group. A reduction in

function and pedometer steps were shown to mitigate bone loss at visit 2 for the TKRs and #<3weeks group respectively. Whilst this initially appears to be counter-intuitive, the measurements for function and activity from the visit preceding the measurement of BMD change had been used in the model to allow for the delayed effects of the explanatory variables. As function and activity, immediately following fracture or surgery, were extremely low for both groups at baseline, minor variations may have caused aberrant results. The mitigating effect of age on bone loss in the control group at visit 4 is contrary to expectations, however this may be explained, in part, to sclerotic effects and degenerative changes in the spine associated with increasing age.

The models for changes in LLTM did not produce any enlightening results. Only three significant explanatory variables were produced, two of which appear to conflict with general assumptions. An increase in the number of co-morbidities mitigated muscle loss in the TKR group at visit 4 whilst an increase in pedometer steps promoted muscle loss in the #<3weeks group at visit 3. Consistent with expectations, increased age of the fracture patients promoted bone loss at visit 4 for the #<3weeks group.

Implications:

The implications of reductions in lower-limb bone and muscle mass may be an increased risk of hip fracture, exacerbated by an additional risk of falls resulting from pain, poor postural stability and muscle weakness. As the TKR group had relatively high mean hip BMD at baseline, the reductions in BMD in absolute terms may not represent a major increase in fracture risk for the average patient, as assessed by tools such as FRAX that use hip BMD as a predictor. However, the disparity between TBS scores and BMD at the lumbar spine suggests that the high BMD in these participants

may not reflect bone quality and structural integrity. An equivalent of TBS is not currently available for use at the hip, although it is in development. If the relationship of TBS and BMD at the spine also applies at the hip, any reduction in hip bone quantity could seriously compromise bone structure and quality in that region and potentially exacerbate fracture risk. This potential disparity between bone quantity and quality at the hip is supported by the AHA results which show a significantly lower hip strength index, 1.33±0.3 ($p=<0.01$) for the TKRs, compared to 1.64±0.4 for the controls, despite BMD values for the TKRs being higher than the controls. The mean values for hip BMD were not significantly different statistically from the control group for either TKR or #<3wks participants, although they appear relatively high in the TKR group. Participants at the lower extreme of both groups, had BMD in the osteopenic or osteoporotic range and many were on prescription (calcium supplements or bisphosphonates + supplements) at varying stages throughout the study. Whilst the mean absolute reduction in bone mass is relatively small, it is important to note that there is a correlation, for both TKR and #<3wks, between bone density at baseline and absolute loss of density at visit 2, $r=0.26$ (n.s) and $r=0.57$ (n.s) respectively. Participants with the lowest bone density at baseline lose more absolute BMD than those with high BMD (Fig.6.23) and therefore, in percentage terms, lose proportionately even more. There is an exponential relationship between BMD and fracture risk such that an equivalent absolute reduction in bone mass in participants with low BMD values, causes a proportionately greater increase in fracture risk than for a participant with higher BMD. Any bone loss may therefore present a substantial increase in hip fracture risk for participants with pre-existing low hip BMD. Lower muscle mass has implications for general function, mobility and risk of falls (203, 207) that may further increase hip fracture risk. As the initial reduction in muscle mass was not restored at the end of the

study in the TKR group, and both TKRs and #<3wks participants had lower muscle mass compared to the controls at visit 4, this may have an additional impact on their susceptibility to future hip fracture over and above any loss in hip BMD. The combination of reduced BMD and muscle atrophy may explain the increased incidence of hip fractures in the year following knee replacement reported by Prieto-Alhambra et al (210). Fracture risk may be further exacerbated by the high BMI of this patient category due to the greater impact forces on the leg bones during weight-bearing activity (161, 162), although obesity has been observed to have a protective effect against hip fracture, possibly related to reduced impact during falls from soft tissue padding in the hip region (269).

The two fracture groups shared a trait of higher rates of previous fracture compared to the other two groups. The BMD results for the newly fractured group were not however consistent with the results from the cross-sectional study of patients who sustained their fractures in the recent past. The former group had recovered losses in hip BMD by the end of the study reaching levels close to, or above, the contralateral leg and not significantly different to the controls. In contrast, at a mean interval of 3.2±2.5 years after injury, the #>1yr group had significant deficits in BMD at all sites, relative to the controls, with the exception of the contralateral total hip, greater trochanter and femoral shaft. They also demonstrated significantly lower scores in all AHA parameters, on both ipsi- and contralateral sides. If these participants retain a long-term deficit in bone density on the ipsilateral side, together with reduced levels of function and activity that inhibit restoration of BMD, they may be at heightened risk for future fragility fractures at the hip.

Whilst the implications of bone and muscle losses are evident, the causes are less clear. Parameters of general function and weight-bearing were included in the modelling but were not shown to have statistically significant effects on bone or muscle loss. It should be acknowledged that the sample size used in this study is relatively small. A larger sample is more reliable for detecting significant associations in multiple regression, requiring increasing sample size for each additional predictor variable added to the model (271). It is therefore feasible that more of the independent variables would have been shown to have significant associations with the outcome variables had the sample size been larger; and whilst the multiple regression models are valid for the sample, they may not necessarily be generalisable to a population model. Although the results from the multiple regression analysis were far from clear or consistent, bisphosphonate use appeared, predictably, to be the best explanatory factor for change in BMD at the total hip, showing (overall) a mitigating effect on bone loss. This supports the findings of Prieto-Alhambra et al (213) who demonstrated a 50-55% reduction in hip fracture incidence following TKR amongst participants using post-surgical bisphosphonate treatments.

Limitations:

As discussed in the previous chapter, the sample used in this study was 100% of white Caucasian ethnicity coming from a rural catchment area in the Southwest of England. Control participants frequently appeared to come from backgrounds of relative affluence and good education that are generally associated with healthier lifestyles; the complete absence of smokers and the high results for activity levels supported this assumption. Participants may not therefore be fully representative of the broader population. To be equivalent to the population used for the NHANES database, on

which DXA diagnostics are based, control participants would exhibit mean Z-scores of zero. However the mean Z–scores for contralateral and ipsilateral total hip BMD, and for lumbar spine BMD, were 0.66, 0.64 and 0.96 respectively (Table 6.4), indicating that they were above average in terms of densitometry results. Nevertheless, they represented the typical population for the catchment area of the study and were therefore an appropriate control for the other groups. Caution should be used however in generalising results to a wider population.

A further limitation was the size of the #< 3 wks group. Due to recruitment difficulties, this group was smaller than anticipated and the analyses of results may be underpowered. Caution should therefore be used when interpreting results and this may account, in part, for the differences between this and the #>1yr group.

Whilst the groups were well matched in the majority of baseline characteristics, the TKRs were a distinct category in terms of significantly higher BMI. There is a known association of BMI with BMD that may be a confounding factor, possibly accounting for some of the variation in BMD compared to the controls. As the study was primarily concerned with monitoring 'within group' changes, no adjustment was made for BMI. BMI has however been included as an independent variable in the multiple regression analysis to account for it as an explanatory factor. Obesity has also been shown to affect precision error in repeat measurements of BMD and TBS as discussed in chapter 2. The effects of this are most relevant for BMD measurements at the spine and are of minimal significance for TBS or BMD measurements of the hip. As no changes of any consequence occurred at the lumbar spine in any of the groups, this issue has not been addressed and is not thought to have affected the outcomes from the study.

7.6 CONCLUSION

The consequences of immobilization, following leg fracture or surgery, were an immediate loss of ipsilateral bone mass at the hip. Whilst these results were not statistically significant for bone loss at the NOF in the #<3wks group, this lack of significance may be due in part to the small numbers in this group. This bone loss was accompanied by bilateral muscle atrophy in the case of knee replacement patients, associated with minor fluctuations in fat mass. Although bone losses at the total hip were subsequently followed by recovery in fracture patients, returning to baseline values, or above, at the end of one year, TKR participants continued a gradual loss over the following 6 months and maintained that loss one year after surgery. This pattern of loss and recovery was replicated in the results for leg muscle loss in the TKRS who completed the study with bilateral deficits in LLTM compared to their baseline measurements, and below the levels for the control group. The potential consequences of these reductions in hip BMD are an increased risk of hip fracture that may be exacerbated by muscle loss/weakness that could affect patients' gait and postural stability thereby increasing the risk of falls. As the TKR group had relatively high mean hip BMD at baseline, the reductions in BMD in absolute terms may not represent a major increase in fracture risk as assessed by tools such as FRAX that use hip BMD as a predictor. However, the disparity between TBS scores and BMD at the lumbar spine suggests that the high BMD in these participants does not reflect bone quality and structural integrity; and this disparity may also be reflected in the low hip strength index for this group relative to their hip BMD. Although the mean reduction in bone mass was relatively small in absolute terms, a correlation was found, for both TKR and #<3wks groups, such that participants with the lowest bone density at baseline lost more absolute BMD than those with high BMD. The exponential relationship which exists

between BMD and fracture risk means that an equivalent absolute reduction in bone mass in participants with low BMD values, causes a proportionately greater increase in fracture risk than for a participant with higher BMD. Any bone loss may therefore present a substantial increase in hip fracture risk for participants with pre-existing low hip BMD.

After an initial deterioration in hip BMD and general function, the newly fractured group demonstrated good recovery in physical and functional parameters, returning to levels comparable to the controls at the end of the study. These findings were not however supported by the results for the cross-sectional group who sustained their fractures at a mean interval of 3.2±2.5 years previously. This group scored significantly below the control group in almost all key outcomes suggesting a long-term impairment in function and bone health. It is not possible to state that these impairments are attributable to the consequences of the fracture but these participants present as a distinct group compared to the controls and the #<3weeks group, and the reasons for the differences they exhibit may merit further investigation. The long-term deficit in hip bone density on the ipsilateral side, together with reduced levels of function and activity that inhibit restoration of BMD, may represent a heightened risk for future fragility fractures at the hip in this group.

Results from the multiple regression analysis show that bisphosphonate use is the best overall predictor for change in BMD at the total hip, having a mitigating effect on bone loss. This suggests that prophylactic treatment may benefit patients at the highest risk of hip fracture. DXA screening, before surgery for TKRs or immediately following fracture, would be valuable to identify patients at the greatest risk for bone loss and to

assess the need for treatment. The #>1yr and the TKR groups had higher BMI than the controls, in the overweight and obese categories (as defined by the WHO criteria (254)) respectively, and both might benefit from exercise regimes to improve function and activity generally, and also encourage weight loss to reduce impact forces on the legs.

Future work:

As the recently fractured group used in this study was small and may have been influenced by selection bias, further work would be valuable to assess bone and muscle loss in a larger sample to confirm the validity of the results. It would be desirable to follow up the current cohort of participants at a later stage, of three to five years post baseline, to investigate longer-term changes in BMD and any hip fracture incidence. It would be useful to apply the hip equivalent of TBS (if this is developed in the near future) to the DXA hip scan data already acquired, to see what this reveals about changes in the microstructural properties of trabecular bone at the proximal femur following disuse.

CHAPTER7. RESULTS – MENTAL WELLBEING AND ASSOCIATIONS WITH PARAMETERS OF FUNCTIONAL RECOVERY AND BONE QUALITY

7.1 INTRODUCTION AND AIMS

This chapter investigates the prevalence of depression and anxiety in groups of postmenopausal women who have had periods of immobilisation due to leg injury or surgery. Three groups; newly fractured patients, patients with fractures from more than one year previously, and total knee replacement patients are compared to an age matched control group. Mental wellbeing at baseline and changes over the twelve month study period are investigated, and associations with parameters of pain, perceived health state, activity levels, physical function and co-morbidities assessed.

Sudden injury or the need for surgery invariably impact on patient's lives and depending upon their personal circumstances (work, family commitments etc.) may cause major disruption to their normal activities, potentially resulting in cumulative stress beyond the physical pain and discomfort associated with the injury or pathology itself. Some level of anxiety, and a sense of loss of control, is highly probable for people who require medical services and/or hospitalisation (272). Participants requiring knee replacement surgery will have endured some degree of chronic pain and disability prior to their surgery that will have inevitably affected their levels of physical function and quality of life. Co-morbidities, reliance on medication and dependence on help from family, friends or outside sources, may be the cause of further distress. In many instances, people's livelihoods are severely affected by limitations in their physical ability to continue their existing occupation with financial

implications that may further impact on their wellbeing (273). Improvement in physical function is often the primary measure of patient outcomes, although it is recognised that psychological factors also influence outcomes of TKR (274). A systematic review by Vissers et al (275) found strong evidence that, in short-term follow-ups of less than one year, postoperative function was not influenced by preoperative depression; however in long-term follow-up, lower preoperative mental health was associated with poorer function and pain scores. It is unclear whether preoperative depression and anxiety contribute to, or result from, knee pain (276). Pain may persist for protracted periods after injury or surgery. A study of 632 TKR patients by Wylde et al (109) found that, 3-4 years after surgery, 44% of patients experienced persistent pain of a varying degree of severity, with 15% suffering severe or extreme pain. In the latter group, an association was found between major depression, additional pain problems elsewhere and post-surgical pain. Depression and anxiety are common in the general population and may be particularly prevalent in the age group represented in this study due to physiological and sociological factors associated with menopause, aging and declining health (277). By comparing the prevalence of depression and anxiety in the patient groups to the controls, information is sought to establish the additional impact of injury or surgery on mental wellbeing and the associations of mental health with physical and functional recovery rates.

In addition to the effects of depression and anxiety on functional recovery after injury or surgery, depression is a condition that is significantly associated with low BMD (101-103). The reasons for this association are highly complex involving a number of factors independent of the effects of reduced weight-bearing activity that result from limited function and activity. Depression may cause a number of behavioural responses which are risk factors for secondary osteoporosis e.g. increased smoking or alcohol consumption, poor diet and a more sedentary lifestyle that may limit exposure to sunlight with consequent reduction in

vitamin D levels (105). Changes in the bone remodelling balance may be attributable in part to hormonal changes during depressive episodes including increased plasma cortisol levels resulting from stress (106). Pharmacological treatments for depression, i.e. selective serotonin reuptake inhibitors (SSRIs), have also been shown to contribute to reduced BMD due to their action on the seratonin system, which is thought to have a regulatory effect on bone mass (104, 105).

The effects of pain and post-surgical nerve damage and their implications for bone loss are discussed in Chapter 1 section 1.3.3. As both pain and depression have been demonstrated to be significant problems for patients following injury or surgery, these factors merit further investigation to assess their impact on bone loss and fragility.

7.2 OBJECTIVES

This chapter investigates:

- Differences between groups, at baseline and during recovery in:
    - Levels of depression and anxiety measured by PHQ-9 and GAD-7 questionnaires.
    - Rates of clinical levels of depression & anxiety assessed by scores of PHQ-9>9 and GAD-7>7.
- Associations between depression & anxiety and parameters of functional recovery.
- Associations between depression & anxiety and bone loss at the ipsilateral total hip.
- Differences in recovery between participants with sub-clinical levels of depression or anxiety and those with clinical levels will be considered.

7.3 BRIEF METHODS AND & STATISTICS

The methods are described in detail in Chapter 2, section 2.2.3. Statistical methods are described in Chapter 2, section 2.3.4.

Data were analysed for all participants who completed the 1 year study. Analysis of subgroups was based on participants with sub-clinical levels of depression or anxiety and those with clinical levels. These groups were classified by the following thresholds (278):

PHQ-9 scores above 9 are considered to represent clinical level depression.

GAD-7 scores above 7 are considered to represent clinical level anxiety.

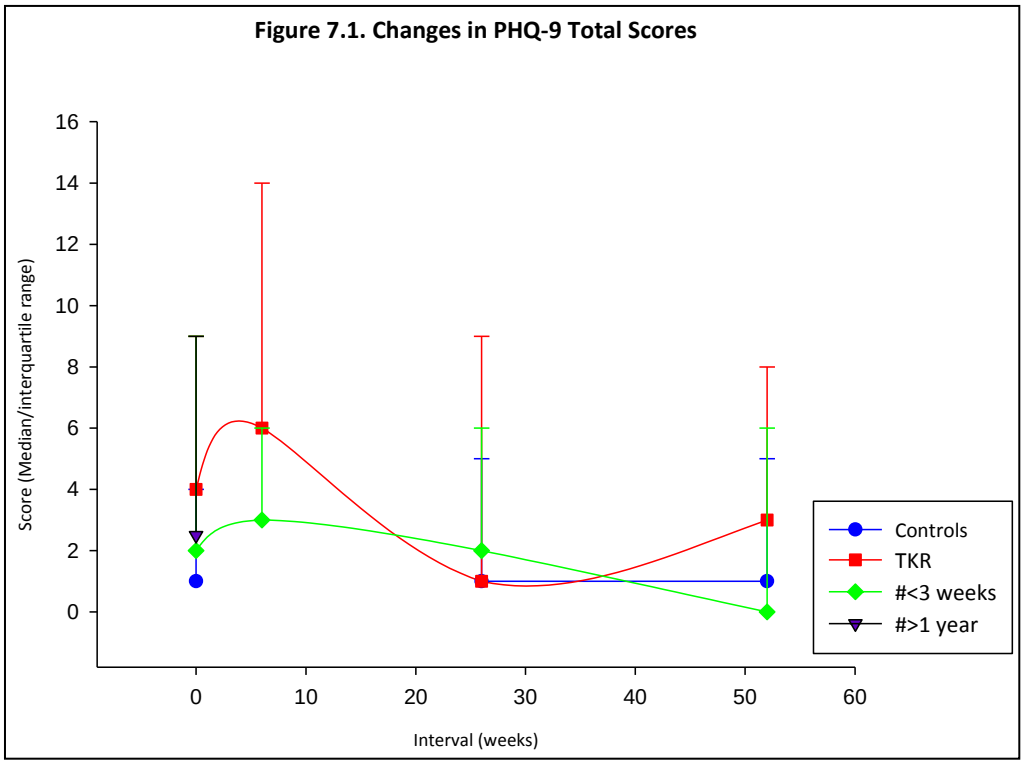
7.4 RESULTS

7.4.1 DESCRIPTIVES

Participant characteristics and results for parameters of physical, functional, emotional recovery and densitometry are reported in chapters 5 and 6, Tables 5.1, 5.3, 5.6, 5.7, 5.8, 6.2 and 6.3.

7.4.2 CHANGES IN DEPRESSION SCORES OVER 1 YEAR - PHQ-9

Figure 7.1 shows the changes in depression scores, assessed by the PHQ-9 questionnaire over the twelve month study period, expressed as medians/inter-quartile range. The maximum possible score for the PHQ-9 is 27. Significances of differences between groups and of changes within groups over the study period are recorded in Chapter 5, Table 5.8; and reported in the following text where appropriate.

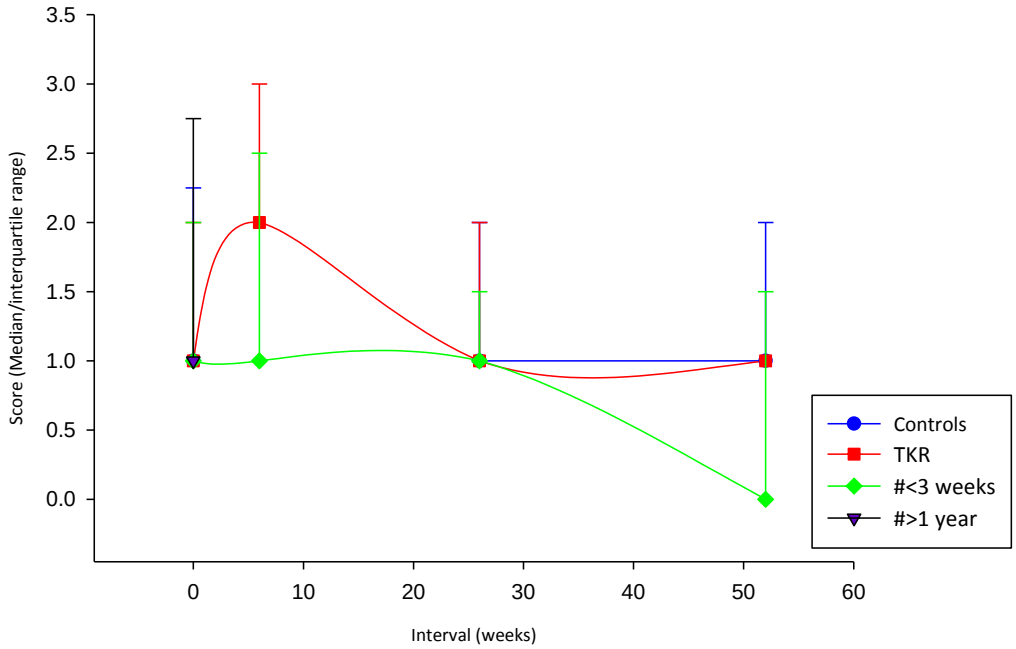


The scores at baseline were highest in the TKR, #>1yr and #<3wks groups, 4.0 and 2.5 and 2.0 respectively, compared to 1.0 in the control group. Differences across the groups were not statistically significant at the 0.05 level using Fisher's exact test for non-parametric data. The control group started the study at low levels of depression and remained stable over the course of one year. Median depression worsened in the TKR and #<3wks groups at the 6 week visit with PHQ-9 scores increasing to 6.0 (n.s) and 3.0 (n.s) respectively. These scores declined as the study progressed and the TKRs completed visit 4 at a level significantly below their baseline (3, p=<0.05) but remaining higher than the controls (n.s) and the #<3wks group.

Figure 7.2 shows the changes in depression level of difficulty scores, assessed by the PHQ-9 questionnaire over the twelve month study period, expressed as medians/inter-quartile range.

The significance of differences between groups and in changes over the study period is recorded in Chapter 5, Table 5.8; and reported in the following text where appropriate. Participants were asked to rate the extent to which their experience of depression affected their lives in terms of difficulty. A score of zero = no depression reported, 1= depression but not causing any difficulty, 2= depression causing some difficulty, 3= depression causing substantial difficulty and 4= depression causing extreme difficulty.

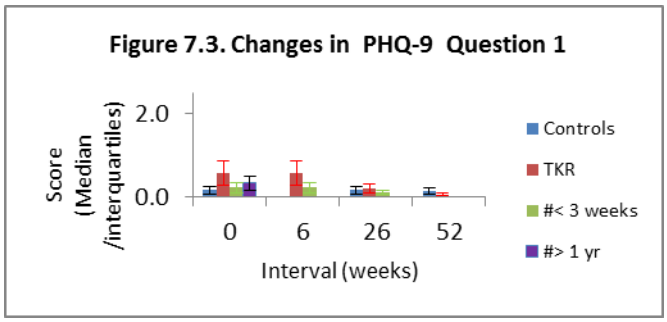
Figure 7.2. Changes in PHQ-9 Difficulty Scores



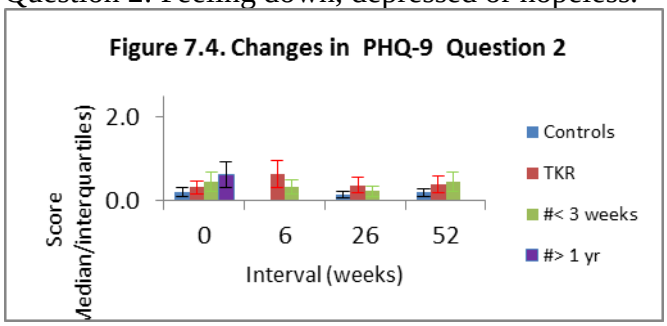
Despite the differential in the depression scores between groups at baseline, the median difficulty scores were low, and the same for all groups (1.0, n.s). Although difficulty increased initially for the TKR group, this returned to the same levels as the other groups at the 6 month visit.

Figures 7.3 to 7.11 show the depression scores and changes over the study period for the individual domains of the PHQ-9 questionnaire (questions 1-9) expressed as median/interquartile range. The score for each domain ranges from 0 to 3.

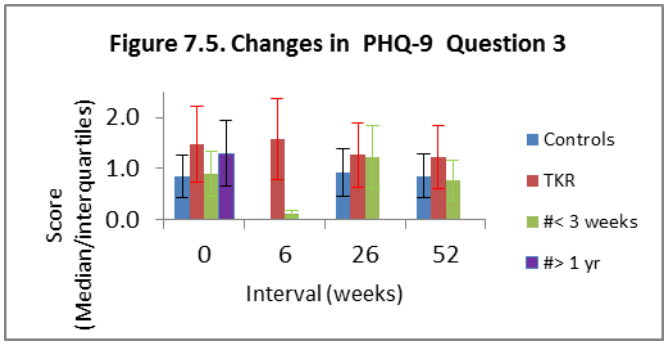
Question 1: Interest and pleasure in doing things.



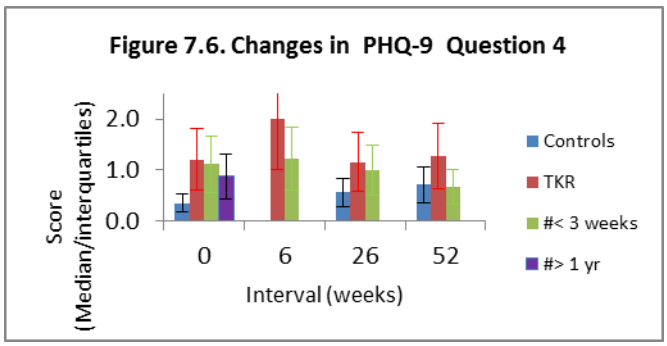
Question 2: Feeling down, depressed or hopeless.



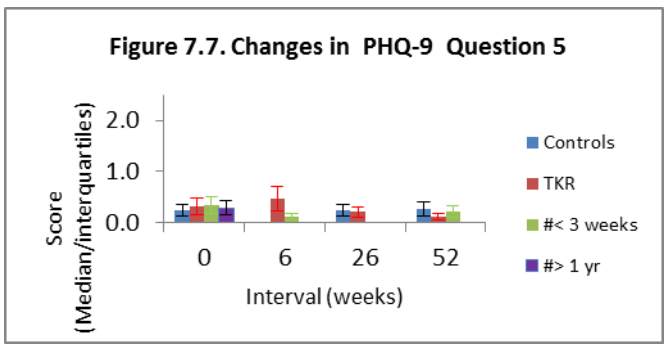
Question 3: Trouble with sleep



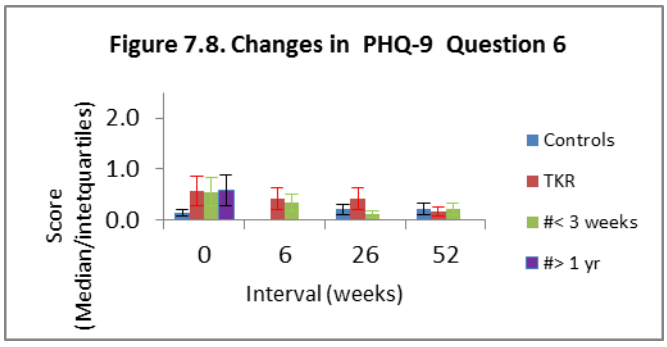
Question 4: Feeling tired or having little energy



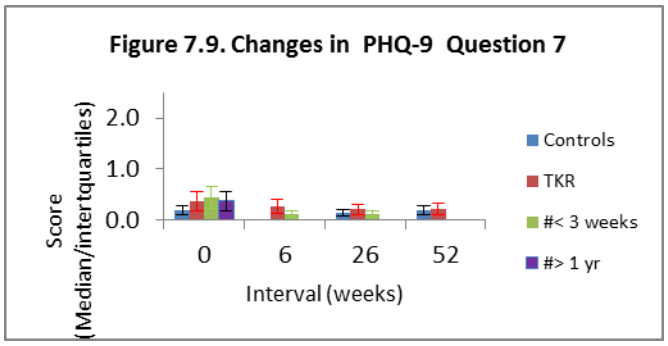
Question 5: Poor appetite or overeating.



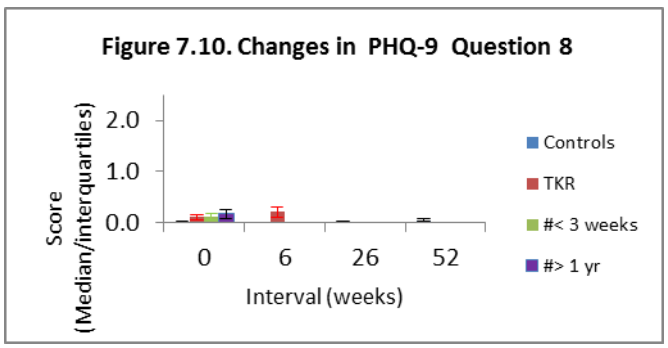
Question 6: Feeling bad about oneself or that one is a failure or has let one's family down



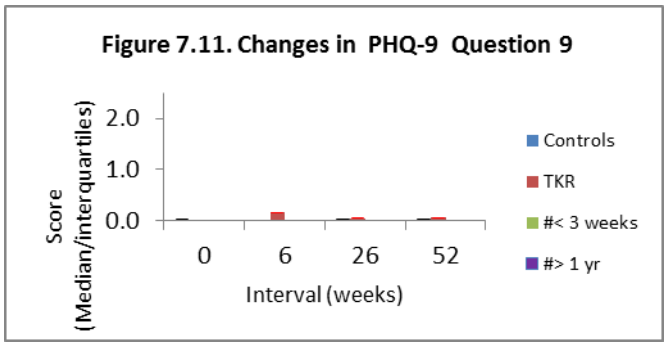
Question 7: Trouble concentrating.



Question 8: Slowness in speech or movement, or restlessness.



Question 9: Thoughts that one would better off dead or hurting oneself.

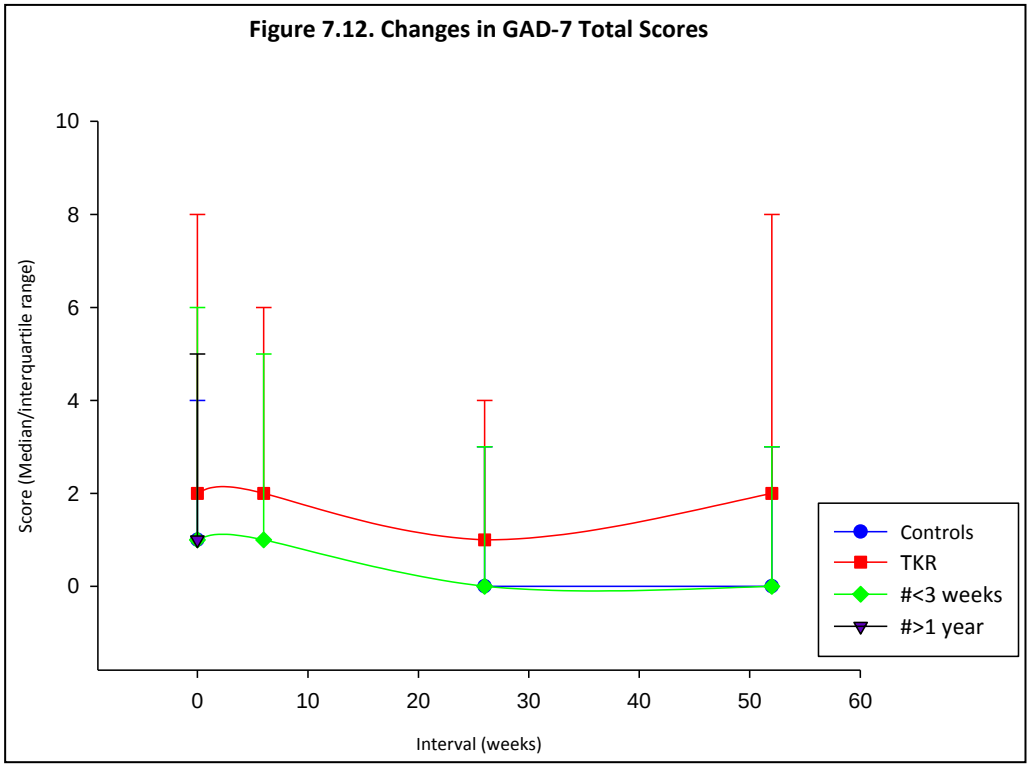


The results for the individual domains of the PHQ-9 questionnaire demonstrate that the highest scores for all groups at baseline related to trouble sleeping together with feelings of tiredness and lack of energy; the highest scores were in the TKR group. The Pearson correlation for pain and sleep problems, for the entire study population at the baseline visit, was r=18.9%, n.s. The longitudinal pattern of initial deterioration and subsequent recovery demonstrated for the PHQ-9 total scores was also reflected (overall) in the individual domains.

7.4.3 CHANGES IN ANXIETY SCORES OVER 1 YEAR - GAD-7

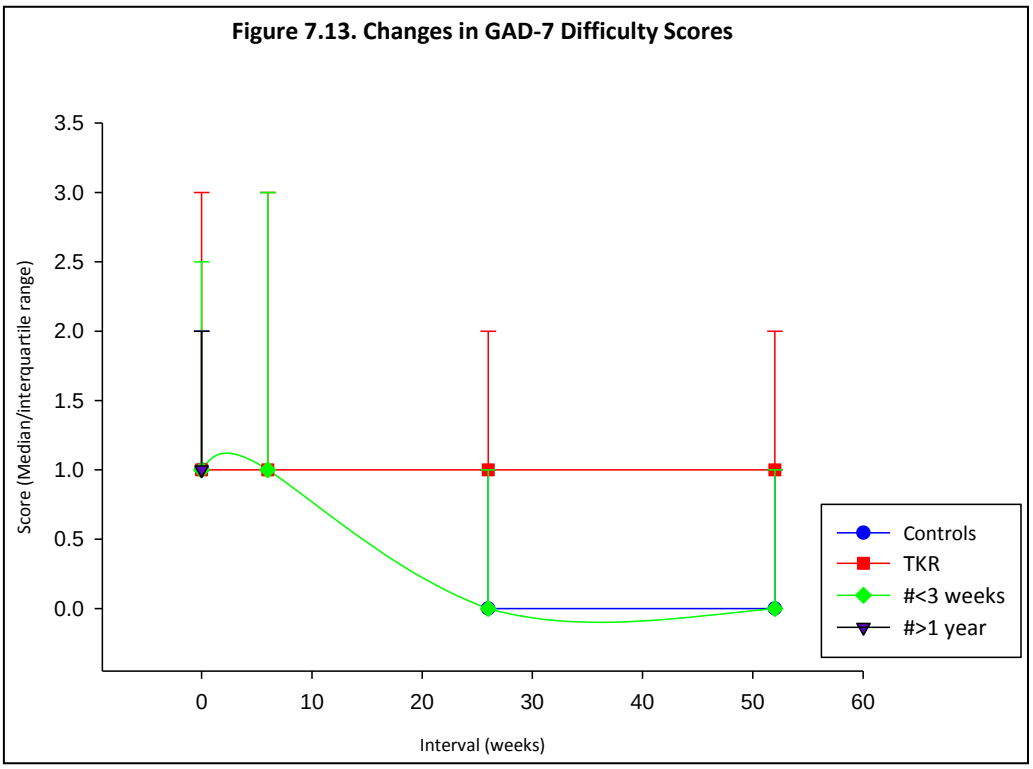
Figure 7.12 shows the changes in anxiety scores, assessed by the GAD-7 questionnaire over the twelve month study period expressed as median/interquartile range. The maximum possible score for the GAD-7 is 21. The significance of differences between groups and in changes over the study period is recorded in Chapter 5, Table 5.8; and reported in the following text where appropriate.

Figure 7.12. Changes in GAD-7 Total Scores



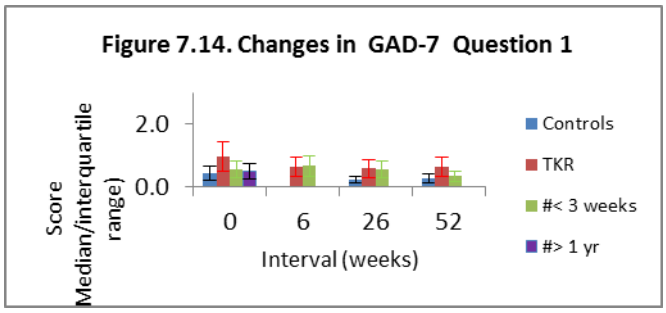
The GAD-7 total scores at baseline were highest in the TKR group (2.0, n.s), but the same for the remaining groups (1.0, n.s). Median anxiety scores were lower than depression scores for all groups at the outset of the study and changes throughout the year were not statistically significant.

Figure 7.13 shows the changes in anxiety level of difficulty scores, assessed by the GAD-7 questionnaire over the twelve month study period, expressed as median/interquartile range. The significance of differences between groups and in changes over the study period is recorded in Chapter 5, Table 5.8; and reported in the following text where appropriate. Participants were asked to rate the extent to which their experience of anxiety affected their lives in terms of difficulty. A score of zero = no anxiety reported, 1= anxious but not causing any difficulty, 2= anxiety causing some difficulty, 3= anxiety causing substantial difficulty and 4= anxiety causing extreme difficulty.

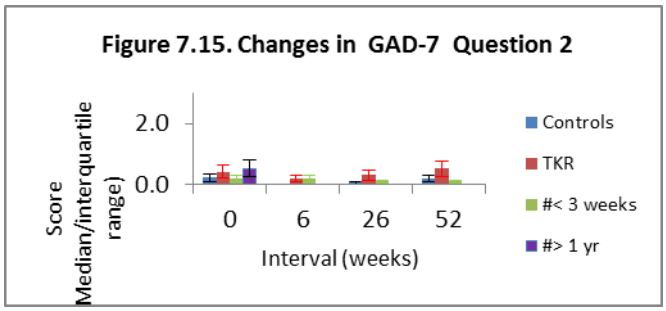


The median scores for difficulty associated with symptoms of anxiety, were low at baseline and the same for all groups (1.0, n.s); scores did not change significantly throughout the one year period.

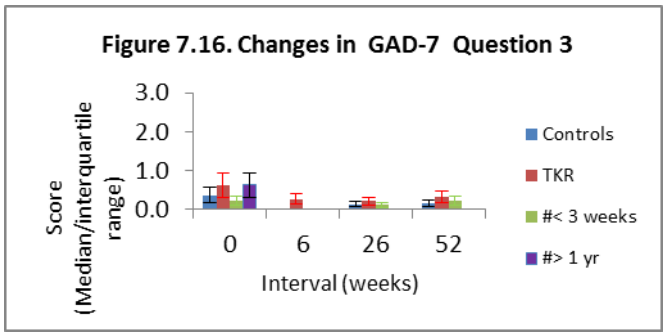
Figures 7.14 to 7.20 show the anxiety scores and changes over the study period for the individual domains of the GAD-7 questionnaire (questions 1-7) expressed as median/interquartile range. The score for each domain ranges from 0 to 3.



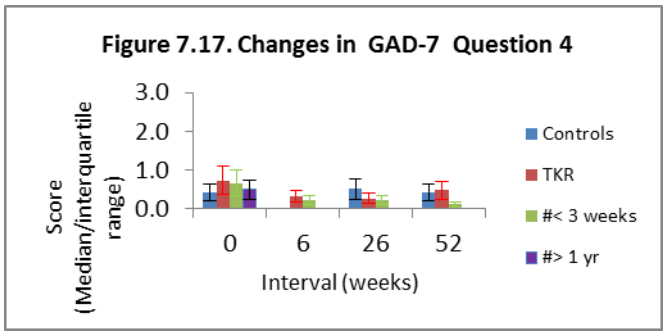
Question 1: Feeling nervous, anxious or on edge.



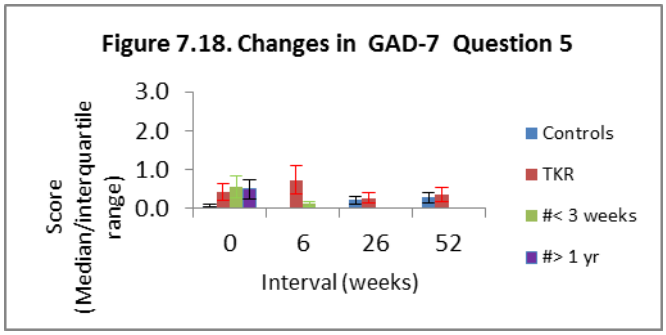
Question 2: Not being able to stop or control worrying.



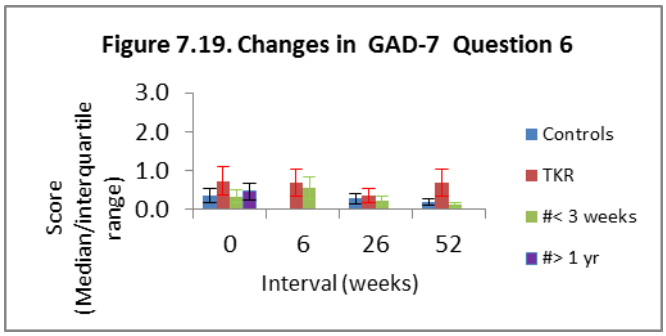
Question 3: Worrying too much about different things.



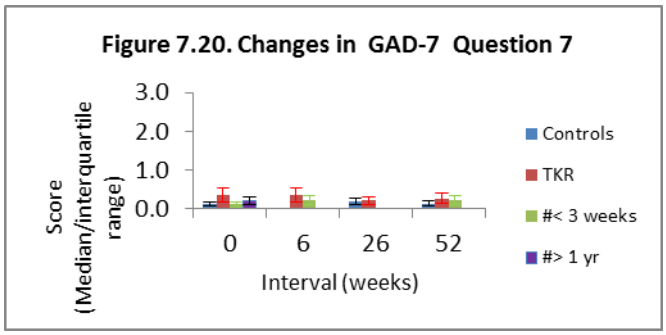
Question 4: Trouble relaxing.



Question 5: Being so restless that it's hard to sit still.



Question 6: Becoming easily annoyed or irritated.



Question 7: Feeling afraid as if something awful might happen.

The results for the individual domains of the GAD-7 questionnaire demonstrate comparable scores for all aspects of anxiety, although relatively minimal with regard to "feeling afraid as if something awful might happen".

7.4.4 RELATIONSHIP BETWEEN DEPRESSION AND PARAMETERS OF PHYSICAL AND FUNCTIONAL RECOVERY

Stepwise multiple regression analysis was performed to create a model of significant explanatory factors for depression as the dependent variable at each time point during the study, baseline (visit 1), 6 weeks (visit 2), 6 months (visit 3) and 1year (visit 4). The independent variables added into the model were:

GAD7 Total score

EQ5D Health state VAS

Age

Pain VAS

LEFS Score

Pedometer average steps per day

Number of falls in the preceding 6 months (or since last visit)

Total of all co-morbidities

BMI

The resulting model summaries for each time point are shown in Tables 7.1 to 7.5 and reported below:

VISIT 1

Table 7.1. Model Summary: Dependent variable – PHQ-9 Depression score at visit 1

Group	Model	R	R Square	Adjusted R Square
Controls	1	.687[a]	0.472	0.457
TKR	1	.820[a]	0.673	0.651
#<3wks	1	.864[b]	0.747	0.711
	2	.967[c]	0.936	0.914
#>1yr	1	.870[a]	0.757	0.743
	2	.928[d]	0.861	0.845

a. Predictors: (Constant), GAD-7 Total score 1

b. Predictors: (Constant), EQ-5DHealth state VAS 1

c. Predictors: (Constant), EQ-5DHealth state VAS 1, Pedometer Average visit 1

d. Predictors: (Constant), GAD-7 Total score 1, Previous falls (not including baseline injury)

Controls: Model 1 was an acceptable fit describing 47.2% of variance in the PHQ-9 depression score at visit 1 (R^2_{adj}= 45.7%), statistical significance $F_{1,17}$= 33.02, p=0.000. With other variables held constant, depression score at visit 1 was positively related to GAD-7 anxiety scores at visit 1, increasing by 0.895 points for every extra anxiety point (t=5.75, p=0.000).

Depression = 0.508 + 0.895 anxiety (Eq.7.1)

TKR: Model 1 was a good fit describing 67.3% of variance in the PHQ-9 depression score at visit 1 (R^2_{adj}= 65.1%), statistical significance $F_{1,15}$= 30.81, p=0.000. With other variables held constant, depression score at visit 1 was positively related to GAD-7 anxiety scores at visit 1, increasing by 1.068 points for every extra anxiety point (t=5.55, p=0.000).

Depression = 1.420 + 1.068 anxiety (Eq.7.2)

#<3 weeks: Model 2 was a very good fit describing 93.6% of variance in the PHQ-9 depression score at visit 1 (R^2_{adj}= 91.4%), statistical significance $F_{2,6}$= 43.54, p=0.000. With other variables held constant, depression score at visit 1 was negatively related to the EQ5D health score at visit 1 decreasing by 0.126 points for every extra health score point at visit 1 (t= -4.91, p=0.003), and positively related to average daily pedometer scores at visit 1, increasing by .002 points for every extra step (t=4.19, p=0.006).

Depression = 9.112 – 0.126 health state + 0.002 pedometer steps (Eq.7.3)

#>1yr: Model 2 was a very good fit describing 86.1% of variance in the PHQ-9 depression score at visit 1 (R^2_{adj}= 91.4%), statistical significance $F_{2,17}$= 52.62, p=0.000. With other variables held constant, depression score at visit 1 was positively related to the GAD-7 anxiety score and the total of previous falls in the previous 6 months, increasing by 1.006 points for every extra anxiety point at visit 1 (t= -9.38, p=0.000), and by 2.509 points for every extra fall (t=3.57, p=0.002).

Depression = 0.601 + 1.006 anxiety + 2.509 falls (Eq.7.4)

VISIT 2

Table 7.2. Model Summary: Dependent variable – PHQ-9 Depression score at visit 2

Group	Model	R	R Square	Adjusted R Square
TKR	1	.636[a]	0.404	0.369
	2	.764[b]	0.584	0.532
#<3wks	1	.891[c]	0.793	0.764
	2	.952[d]	0.907	0.875

a. Predictors: (Constant), GAD-7 Total score 2

b. Predictors: (Constant), GAD-7 Total score 2, Pain VAS 2

c. Predictors: (Constant), LEFS Score 2

d. Predictors: (Constant), LEFS Score 2, Total all comorbidities

Controls: Not applicable.

TKR: Model 2 was a good fit describing 58.4% of variance in the PHQ-9 depression score at visit 2 (R^2_{adj}= 53.2%), statistical significance $F_{2.16}$= 11.23, p=0.001. With other variables held constant, depression score at visit 2 was positively related to GAD-7 anxiety score and pain score a visit 2, increasing by 1.140 points for every extra anxiety point (t=4.44, p=0.000) and 0.088 points for every extra pain score point (t=2.63, p=0.018).

Depression = -0.119 +1.140 anxiety + 0.88 pain (Eq.7.5)

#<3 weeks: Model 2 was a very good fit describing 90.7% of variance in the PHQ-9 depression score at visit 2 (R^2_{adj}= 87.5%), statistical significance $F_{2.6}$= 29.11, p=0.001. With other variables held constant, depression score at visit 2 was negatively related to LEFS at visit 2 and total co-morbidities, decreasing by 0.111 points for every extra LEFS point (t= -7.50, p=0.000) and 0.716 points for every extra co-morbidity (t=2.70, p=0.036).

Depression = 7.831 – 0.111 LEFS – 0.716 co-morbidities (Eq.7.6)

#>1yr: Not applicable.

VISIT 3

Table 7.3. Model Summary: Dependent variable – PHQ-9 Depression score at visit 3

Group	Model	R	R Square	Adjusted R Square
Controls	1	.613[a]	.375	.359
TKR	1	.784[b]	.615	.592
	2	.871[c]	.759	.729
#<3wks	1	.757[d]	.573	.512

a. Predictors: (Constant), GAD-7 Total score 3
b. Predictors: (Constant), EQ-5DHealth state VAS 3
c. Predictors: (Constant), EQ-5DHealth state VAS 3, TOTAL ALL comorbidities
d. Predictors: (Constant), Falls 3 coded

Controls: Model 1 was an acceptable fit describing 37.5% of variance in the PHQ-9 depression score at visit 3 (R^2_{adj}= 35.90%), statistical significance $F_{1,39}$= 23.439, p=0.000. With other variables held constant, depression score at visit 3 was positively related to anxiety, increasing by 0.816 points for every extra GAD-7 point (t=4.84, p=0.000).

Depression = 1.195 + 0.816 anxiety (Eq.7.7)

TKR: Model 2 was a very good fit describing 75.9% of variance in the PHQ-9 depression score at visit 3 (R^2_{adj}= 72.9%), statistical significance $F_{2,16}$= 25.182, p=0.000. With other variables held constant, depression score at visit 3 was positively related to total number of all co-morbidities increasing by 1.331 points for every extra co-morbidity (t= 3.10, p=0.007), and negatively related to EQ5D health scores at visit 3, decreasing by 0.201 points for every extra health point (t= -6.030, p=0.000).

Depression = 16.192 + 1.331 co-morbidity – 0.201 health state (Eq.7.8)

#<3 weeks: Model 1 was a good fit describing 57.3% of variance in the PHQ-9 depression score at visit 3 (R^2_{adj}= 52.1%), statistical significance $F_{1.7}$= 9.389, p=0.018. With other variables held constant, depression score at visit 3 was positively related to number of falls in the previous 6 months increasing by 5.875points for each extra fall (t= 3.06, p=0.018).

$$\text{Depression} = 2.125 + 5.875 \text{ falls} \qquad \text{(Eq.7.9)}$$

#>1yr: Not applicable.

VISIT 4

Table 7.4. Model Summary: Dependent variable – PHQ-9 Depression score at visit 4

Group	Model	R	R Square	Adjusted R Square
Controls	1	.592[a]	0.35	0.332
	2	.705[b]	0.498	0.47
	3	.750[c]	0.562	0.524
TKR	1	.801[a]	0.642	0.609
	2	.874[d]	0.764	0.717
#<3wks	1	.968[a]	0.938	0.929

a. Predictors: (Constant), GAD-7 Total score 4

b. Predictors: (Constant), GAD-7 Total score 4, Age

c. Predictors: (Constant), GAD-7 Total score 4, Age, EQ-5DHealth state VAS 4

d. Predictors: (Constant), GAD-7 Total score 4, EQ-5DHealth state VAS 4

Controls: Model 3 was a good fit describing 56.2% of variance in the PHQ-9 depression score at visit 4 (R^2_{adj}= 52.4%), statistical significance $F_{3.35}$= 14.965, p=0.000. With other variables held constant, depression score at visit 4 was positively related to GAD-7 anxiety score at visit 4 and age, increasing by 0.820 points for each extra Gad-7 point (t= 4.99, p=0.000) and by 0.176 points for each extra year in age (t= 3.32, p=0.002) . It was negatively related to EQ5D health score at visit 4 decreasing by 0.71 points for every extra health point (t= -2.27, p=0.030).

Depression = 4.009 + 0.820 anxiety + 0.176 age – 0.71 health state (Eq.7.10)

TKR: Model 2 was a very good fit describing 76.4% of variance in the PHQ-9 depression score at visit 4 (R^2_{adj}= 71.7%), statistical significance $F_{2,10}$= 16.19, p=0.001. With other variables held constant, depression score at visit 4 was positively related to GAD-7 anxiety score at visit 4 increasing by 0.329 points for every extra GAD-7 point (t= 3.47, p=0.006). It was negatively related to EQ5D health scores at visit 4, decreasing by 0.098 points for every extra health point (t= -2.28, p=0.046).

Depression = 10.120 + 0.329 anxiety – 0.098 health state (Eq.7.11)

#<3 weeks: Model 1 was a very good fit describing 93.8% of variance in the PHQ-9 depression score at visit 4 (R^2_{adj}= 92.9%), statistical significance $F_{1,7}$= 105.41, p=0.000. With other variables held constant, depression score at visit 4 was positively related to GAD-7 anxiety score at visit 4 increasing by 1.714 points for every extra GAD-7 point (t= 10.27, p=0.000).

$$\text{Depression} = 0.429 + 1.714 \text{ anxiety} \qquad \text{(Eq.7.12)}$$

#>1yr: Not applicable.

Table 7.5. Simplified summary of multiple regression analysis
Significant explanatory factors (from same visit) for Depression (PHQ-9 score)

	Controls	TKR	#<3 wks	#>1yr
Visit 1	↑ GAD-7 anxiety	↑ GAD-7 anxiety	↓ EQ5D health ↑ pedometer	↑ GAD-7 anxiety ↑ previous falls
Visit 2		↑ pain ↑ GAD-7 anxiety	↓ LEFS ↓ co-morbidities	
Visit 3	↑ GAD-7 anxiety	↑ co-morbidities ↓ EQ5D health	↑ previous falls	
Visit 4	↑ GAD-7 anxiety ↑ age ↓ EQ5D health	↑ GAD-7 anxiety ↓ EQ5D health		

↑ indicates an increase in PHQ-9 score, i.e. decline in depression state, as the score for the independent variable increases
↓ indicates decrease in PHQ-9 score i.e. improvement in depression state, as the score for the independent variable increases

7.4.5 RELATIONSHIP BETWEEN BONE AND LOSS AND DEPRESSION

Stepwise multiple regression analysis was performed to assess the contribution of depression and anxiety variables to bone loss at the total hip region as the dependent variable, at three time points during recovery, 6 weeks (visit2), 6 months (visit 3) and 1 year (visit 4). Bone loss at this site was selected as it demonstrated significant change in the TKR group. Although it was expected that there would be some delayed effect on bone loss resulting from depression and anxiety, this has been considered in chapter 6; the independent variables from the same time point as measures of the dependent variable were therefore used in the following models. The independent variables added into the model were:

PHQ9 Total score

GAD7 Total score

The resulting model summaries for each visit are shown in Tables 7.6 to 7.8 and reported below:

VISIT 2

Table 7.6. Model Summary: Dependent variable - Changes in BMD at the ipsilateral total hip at visit 2

Group	Model	R	R Square	Adjusted R Square
#<3wks	1	.819[a]	0.67	0.623

a. Predictors: (Constant), PHQ-9Total score 2

Controls: Not applicable.

TKR: No significant independent variables found.

#<3 weeks: Model 1 was a good fit describing 67.0% of variance in change in total hip BMD at visit 2 (R^2_{adj}= 62.3%), statistical significance $F_{1,7}$= 14.22, p=0.007. With other variables held constant, change in total hip BMD at visit 2 was negatively related to PHQ-9 depression score at visit 2, decreasing by 0.009 g/cm^2 for every extra PHQ-9 point (t= -3.77, p=0.007).

Change in ipsi total hip BMD = 0.012 – 0.009 depression (Eq.7.13)

#>1yr: Not applicable.

VISIT 3

Table 7.7. Model Summary: Dependent variable - Changes in BMD at the ipsilateral total hip at visit 3

Group	Model	R	R Square	Adjusted R Square
Controls	1	.368[a]	.135	.114
#<3wks	1	.845[b]	.714	.673

a. Predictors: (Constant), PHQ-9Total score 3

b. Predictors: (Constant), GAD-7 Total score 3

Controls: Model 1 was a very poor fit describing only 13.5% of variance in change in total hip BMD at visit 3 (R^2_{adj}= 11.4%), statistical significance $F_{1,41}$= 6.42, p=0.015. With other variables held constant, change in total hip BMD at visit 3 was positively related to PHQ-9 depression score at visit 3, increasing by 0.002 g/cm^2 for every extra PHQ-9 point (t= 2.53, p=0.015).

Change in total hip BMD = -0.006 + .002 depression (Eq.7.14)

TKR: No significant independent variables found.

#<3 weeks: Model 1 was a very good fit describing only 71.4% of variance in change in total hip BMD at visit 3 (R^2_{adj}= 67.3%), statistical significance $F_{1,7}$= 17.44, p=0.004. With other variables held constant, change in total hip BMD at visit 3 was negatively related to anxiety at visit 3, decreasing by 0.012 g/cm^2 for every extra GAD-7point (t= -4.18, p=0.004).

$$\text{Change in total hip BMD} = 0.017 - 0.012 \text{ anxiety} \qquad \text{(Eq.7.15)}$$

#>1yr: Not applicable.

VISIT 4

Controls: No significant independent variables found.

TKR: No significant independent variables found.

#<3 weeks: No significant independent variables found.

#>1yr: Not applicable.

Table 7.8. Simplified summary of multiple regression analysis
Significant explanatory factors (from same visit) for change in BMD at the ipsilateral total hip

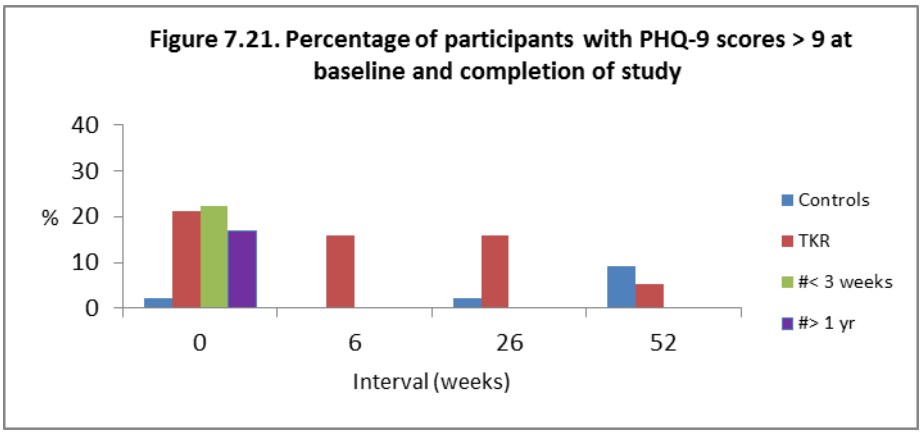
	Controls	TKR	#<3 wks	#>1yr
Visit 1				
Visit 2			↓ PHQ-9 depression	
Visit 3	↑ PHQ-9 depression		↓ GAD-7 anxiety	
Visit 4				

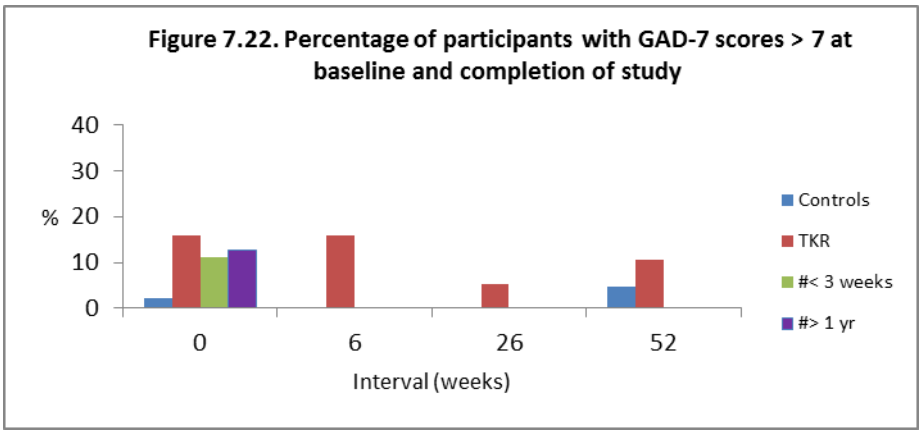
↑ indicates mitigation of BMD loss at the ipsilateral total hip as the score for the independent variable increases
↓ indicate promotion of BMD loss at the ipsilateral total hip as the score for the independent variable increases

7.4.6 SUBGROUP ANALYSIS OF PARTICIPANTS WITH CLINICAL LEVELS OF DEPRESSION AND ANXIETY

As the medians for all groups in depression and anxiety scores were below the levels that would be considered to be of clinical importance, i.e. scores below 9 for PHQ-9 and below 7 for GAD-7, it was considered worthwhile to investigate the prevalence of clinical depression and anxiety in the groups, and to consider if there were any notable differences in the subgroups for relationships between BMD changes and depression.

Figures 7.21 and 7.22 show the percentage of each participant group with depression and anxiety scores at clinical levels, at each stage of the study.





At all stages of the study, prevalence of clinical depression and anxiety are highest in the TKR group, with the exception of visit 1 when the #<3wks group is slightly higher

at 22.2% of the group compared to 21.2% of TKRs. All groups were substantially higher than the controls at baseline (2.3% of group). There were no #<3wks participants with clinical depression or anxiety after the baseline visit. The #>1yr group had a high incidence of both depression and anxiety relative to the controls, 16.8% v 2.3% for clinical depression and 12.6% v. 2.3% for clinical anxiety.

Table 7.9 Participants on antidepressant medication at baseline - visit 1

Controls n=43	TKR n=19	#<3wks n=9	#>1yr n=24
3	0	0	0

Table 7.9 shows that only 3 participants on the study, all in the control group, were on anti-depressant medication.

Figures 7.23 to 7.25 show the relationship between PHQ-9 depression scores and changes in BMD at the ipsilateral total hip, in categories of TKR participants with subclinical and clinical levels of depression, at visits 2, 3 and 4. No differences are apparent at any of the visits, between the groups 'above' and 'below' the clinical depression thresholds.

Figure 7.23. Correlation at Visit 2 between depression scores and change from baseline in BMD at ipsilateral Total Hip

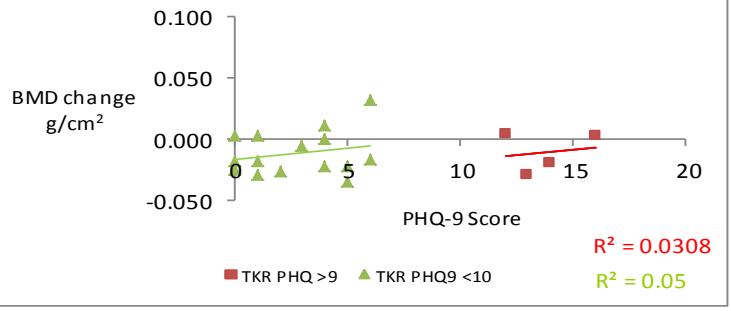


Figure 7.24. Correlation at Visit 3 between depression scores and change from baseline in BMD at ipsilateral Total Hip

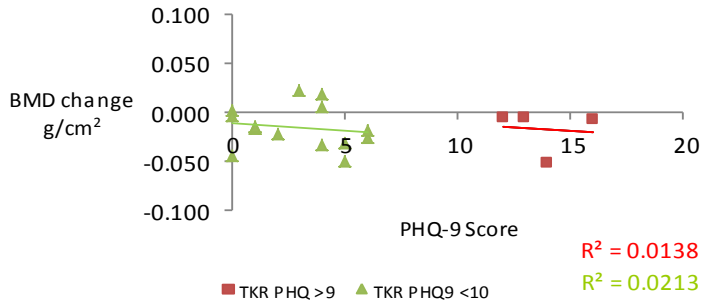
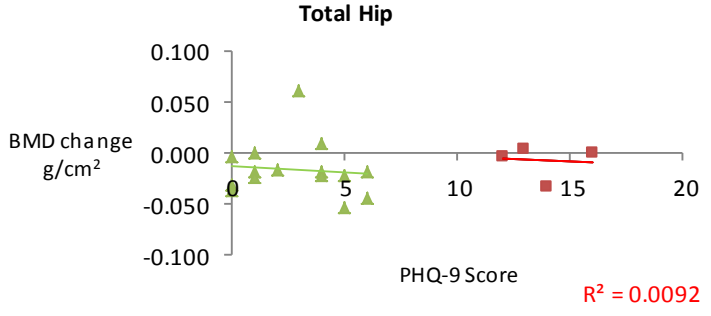


Figure 7.25. Correlation at Visit 4 between depression scores and change from baseline in BMD at ipsilateral Total Hip



7.5 DISCUSSION

Baseline differences between groups and longitudinal changes:

The results (Fig. 7.1) demonstrate that, although differences were not statistically significant between the groups, depression levels at baseline were highest in the TKR group, and that the #>1yr and #<3wks groups were both relatively high compared to the controls. Nevertheless the level of difficulty caused to participants, in their general life, by their depressive symptoms was low, and similar for all groups (Fig. 7.2). The highest scores for all groups at baseline related to trouble sleeping, feelings of tiredness and lack of energy, with the highest scores demonstrated in the TKR group.

Whilst highest in the TKR group, the scores for anxiety at baseline were low and at a comparable level for the remaining groups. The levels of difficulty, caused to participants by their symptoms of anxiety, were the same for all groups (Fig 7.13). The higher anxiety scores for the knee replacement patients may, in part, reflect the anticipation of imminent surgery and hospitalization together with ongoing concerns about their recovery. Despite this, scores for question 7, "feeling afraid as if something awful might happen", were low compared to all other domains of the GAD-7 questionnaire and it is inferred that participants did not suffer any undue sense of fear about the outcomes of their surgery.

Whilst the median depression scores worsened in the TKR and #<3wks groups at the 6 week visit, these scores declined again as the study progressed suggesting an overall improvement as patients started to recover physically and functionally. However, although the TKRs completed visit 4 at a level significantly below their baseline, their depression scores remained higher than the controls and the #<3wks group, indicating that recovery in terms of mental well-being was not complete. The patterns of initial

deterioration and subsequent recovery in depression scores were reflected (overall) in the individual domains for the PHQ-9 questionnaire but problems relating to sleep and tiredness, whilst improved, were unresolved for the TKRs in particular, remaining higher than for the other groups at the end of the study. Problems with sleep correlated poorly with pain and were not statistically significant.

Clinical levels of depression and anxiety:

Although the medians for all groups in depression and anxiety scores were below the levels that would be considered to be of clinical importance, an analysis of subgroups with scores above 9 for PHQ-9 and above 7 for GAD-7, (Figures 7.21 and 7.22) showed a higher prevalence of clinical depression and anxiety at baseline in all patient groups compared to the controls. This situation did not pertain for the #<3wks group beyond the first visit but rates of clinical level depression remained high for the TKR group throughout the study. Although numerous participants would meet the criteria for clinical level depressive symptoms using the thresholds above, only 3 participants on the study (table 7.9), all in the control group, were on anti-depressant medication. The limited numbers of participants on medication suggests that clinical depression, in the study groups, may be clinically under-diagnosed.

Thus far, a picture emerges of generally poorer mental wellbeing in the TKR group. This result might reasonably be expected as it is associated with poor rates of physical recovery compared to the newly fractured patients. The reasons for relatively high rates of depression in the #>1yr group are however less obvious but may be associated with the significantly poorer levels of function and activity compared to controls, as discussed in chapter 5.

Relationship between depression and parameters of physical and functional recovery:

As anticipated, results from the multiple regression analysis (Table 7.5) demonstrated significant relationships between anxiety and depression with a worsening in depression as anxiety increases. This relationship was evident for all groups, and at different stages of the study, with the exception of the #<3wks group. A less obvious association emerged between depression and previous experience of falls in the #<3wks and #>1yr groups. This may involve a complex relationship between depression, poor physical function and fear of falling (265). Pain was a significant factor only for the TKR group at visit 2, alongside a higher number of co-morbidities at visit 3 and reduced perceptions of health at visits 3 and 4. Health state was also a significant factor for the controls and #<3wks groups with worsening depression associated with poorer scores for perceived health state. Increased age was only an explanatory factor for depression in the controls at visit 4. The #<3wks group demonstrated worsening depression with lower pedometer scores at visit 1 and with reduced function scores at visit 2 suggesting that their depression was significantly related to their inability to perform their normal activities early on in their recovery. As many in this group were in employment, these functional problems may have been the cause of greater difficulty than for the TKRs for whom these factors did not appear to be significant. The TKRs would have already been experiencing long-term impairment in their function and activity prior to surgery and may therefore have become more accustomed to their functional limitations, adapting their lifestyles accordingly. The only counter-intuitive relationship that was revealed in the modelling was an improvement in depression with a higher number of co-morbidities in the #<3wk group at visit 2.

Relationship between bone loss and depression:

Depression and anxiety were included as independent variables in a multiple regression analysis, reported in chapter 6, with changes in BMD at the ipsilateral total hip as the dependent variable. In that analysis, independent variables were used from the visit preceding the measurement of BMD change to allow for delayed effects on potential bone loss. It did not reveal any significant relationships of BMD change with depression, and showed only one significant relationship with anxiety in the #<3wks group, for whom bone loss was mitigated at visit 4 as anxiety reduced at visit 3. The results in Table 7.8 report the analysis using depression and anxiety scores from the same visit as the bone change measurements and showed a significant association of depression and anxiety with bone change at visits 2 and 3 respectively for the #<3wks group, whereby bone loss was promoted by an increase in depression and anxiety scores. Although this relationship was reversed in the result for the control group at visit 3, this is nonetheless an interesting result in relation to previous studies which observe an association between depression, decreased BMD and increased fracture risk (101, 105, 279) The sub-analysis of participants with clinical levels of depression (Figs 7.23 to 7.25) show the rates of bone loss, in the TKR group, at the ipsilateral total hip (at visits 2, 3 and 4) as depression scores increase. No differences, at any of the visits, between the 'above' and 'below' clinical depression groups are apparent; however caution should be used in interpreting results from such small samples.

Implications:

It is arguable that, notwithstanding any possible effects of depression on bone loss, psychological recovery from the trauma of injury or surgery is as important as physical

and functional recovery. The interaction of the variables in recovery (pain, function, activity etc.) is complex; depression and anxiety may be either the cause or the result of pain and poor physical or functional outcomes. Depression and anxiety can have a major impact on a patient's quality of life; and mental wellbeing should be considered as both an explanatory variable for physical outcomes and as an outcome measure in its own right.

The control group exhibited substantially lower mean scores for both depression and anxiety compared to the other groups at baseline and this was consistent for the remainder of the study. How well this reflects depression and anxiety in the wider population has not been evaluated and it may be that a bias in research volunteers to have a higher socio-economic status and a better general health background, has influenced the results for this group. Whilst highest in the TKR group, anxiety scores were lower than depression scores for all groups throughout the study. For all groups, the greatest contribution to depression scores was due to sleep problems and tiredness.

There are interesting disparities between the #<3wks and #>1yr groups. The #<3wks group had higher levels of depression and anxiety than the controls at the outset of the study, particularly at their 6 week visit, but recovered to the same levels as the controls, or below, at the finish, suggesting that their symptoms of depression and anxiety were largely related to their poorer physical condition and reduced function levels immediately following injury. This is supported by the results of the multiple regression analysis which demonstrated an increase in depression as pedometer scores reduced at visit 1 and as function scores reduced at visit 2. A very different picture emerged for the #>1yr who, alongside poorer results for physical and functional parameters discussed in chapters 5 and 6, also demonstrated higher levels of depression than either the #<3wks group or the controls at the same time point. The multiple regression analysis

demonstrated that this was associated with anxiety and a previous history of more falls. An increased number of falls in the previous 6 months was also a significant explanatory factor for depression in the #<3wk group at visit 3 and it is possible that this relates to a complex relationship between depression, poor physical function and fear of falling (265) For newly fractured patients, there is little that can be changed in the early stages to improve their functional recovery during the process of fracture healing and reduced weight-bearing, therefore the inevitable frustrations of limited function and activity are unavoidable. As pain does not appear to contribute significantly to depression in this group and most participants are well medicated following injury, there may be limited potential to improve the patient experience in this group other than possibly offering some aids to sleep alongside appropriate exercise strategies, following fracture healing, to improve muscle strength and stability thereby aiding avoidance of falls.

The results for the TKR group demonstrated higher levels of depression and anxiety throughout the study (except for visit 3) and although they showed significant improvement from their baseline scores, they did not return to control levels at the final visit. Clinical levels of depression and anxiety were also highest in this group throughout the study. Results from the multiple regression analysis indicate that depression in this group was significantly associated with pain, poor perceptions of health, a higher number of co-morbidities and anxiety. It is possible that the patient experience and clinical outcomes for the TKR group could be considerably improved. Although there is service provision in the form of advice, physiotherapy and supervised exercise classes, both before and after surgery, the interventions offered to individuals (in the setting of this study) are very inconsistent and the expectations of different

patients, with regard to the speed and extent of their recovery, were very varied. Despite a reluctance of many patients to rely on drugs, improvements in pain levels or sleep problems could be achieved by encouraging adherence to medications or offering alternative, non-pharmaceutical therapies. Depression and anxiety have been identified to have a high incidence in 1,212,413 patients undergoing total joint arthroplasty in the United States between the years of 2000 and 2008. More than one in fourteen patients had a diagnosis of depression, anxiety or both which were associated with higher healthcare costs and resources (107). A small scale study by Caracciolo and Giaquinto (280), including thirty-six TKR patients, showed that 58% were above the Hospital Anxiety and Depression (HAD) threshold and that psychological distress and depression were significantly associated with reduced functional rehabilitation. These studies are consistent with the high incidence of clinical levels of depression and anxiety found in the TKR group from this study, and suggests that a formal assessment for these conditions is indicated whereby patients could benefit from advice or counseling to alleviate their symptoms and potentially improve functional recovery. As the potential for anti-depressant drugs to exacerbate bone loss is a subject of ongoing research, the use of these treatments in this group should be considered with caution. In every regard, patients might benefit from group interventions. Group exercise classes could be a cost-effective option for healthcare services, benefiting patients by improving their function and activity levels whilst also encouraging weight loss. As some association has been shown between bone loss and depression, social networks forged through these groups may afford peer support to aid mental wellbeing and could help patients to have more realistic expectations for their progress in recovery. As use of antidepressant drugs is also thought to be associated with bone loss, opportunities for

peer support or counseling, to avoid the need for pharmaceutical interventions, might also prove valuable in prevention of future hip fractures in these patients.

Limitations:

The study has a number of limitations including the small sample size of the #<3wks group and a potential recruitment bias in the control group that has been discussed in previous chapters. There may also be some bias with the TKRs and #<3wks groups due to their dependence on a support network to participate in the study. The study had a largely rural catchment area and as many participants were required to travel large distances to attend the data collection sessions at a time when they were prohibited from driving, only those patients with appropriate support were able to take part. This suggests that many of them enjoyed a level of social support that may have influenced their general state of wellbeing such that the study results could have underestimated the levels of depression and anxiety in a wider population.

In order to be comparable to the control group, participants were asked to answer questions on depression and anxiety relating to any issues, not solely with regard to their current physical condition. Some of the participants with leg pathology were coincidentally experiencing other major problems in their lives resulting in very high levels of anxiety. They may therefore appear as outliers in the data but reporting the results as median scores will have eliminated these effects.

Subjectivity in responses to questionnaires is always a difficulty in research, particularly with regard to questions that require a rating of levels of pain or perception of health.

Instructions in answering questions were as specific as possible, but some differences in participants' interpretation were unavoidable.

8.6 CONCLUSION

The influences on depression and the patterns of recovery in the various groups were distinct. TKR patients experienced the worst levels of depression and anxiety with the poorest recovery, whilst the newly fractured patients recovered well after an initial period of poor scores following their injury. Depression in the TKR group mostly related to pain, anxiety, a higher number of co-morbidities and poor perceptions of their health, whilst for the #<3wks group it related largely to poorer function, activity and a higher rate of falls. Despite the evident good recovery in the newly fractured group, participants from the cross-sectional arm of the study showed distinctly different results with a relatively high level of depression associated with anxiety and a previous history of more falls. Poor sleep was a key factor for depression in all of the groups but is not significantly related to pain.

A significant association was shown between depression and bone loss in the #<3wks group that supports findings from previous studies that show an association of depression with reduced BMD and increased fracture risk. This may have implications for the treatment of depression in patients following fracture or surgery as the use of antidepressants is also associated with reduced BMD which could exacerbate fracture risk in patients already at risk of bone loss as a consequence of their injury. An analysis of sub-groups, above the thresholds for clinical depression and anxiety, demonstrated the highest levels of both conditions in the TKR group throughout the entire study period. An attempt was made to compare rates of bone loss at the ipsilateral hip between the clinically and non-clinically depressed sub-groups of the TKRs and, whilst

it was a useful exercise, the sample numbers were too small to reliably differentiate between them.

Although the possibilities are more limited for fracture patients, who are required to be immobile during the initial period of fracture healing, cost-effective opportunities may be available to support TKR patients in their recovery via the use of group exercise classes and improved advice and treatment for depression, pain and sleep problems.

Future work:

This study has only provided a fairly superficial overview of the prevalence of depression and anxiety in these participant groups and a more 'in depth' assessment of the causes of these conditions would be valuable. It would be particularly interesting to establish the reasons for higher levels of depression in the #>1yr group and whether these are attributable in any way to the outcomes of their leg fracture.

As the #<3wks group was smaller than desired, further work on a larger sample would be useful to validate the results from this study. Also, the study could be extended to a larger sample of TKR patients to enable an investigation into the effects on bone loss of depression in subgroups above and below clinical thresholds.

Finally, an assessment of the interventions, suggested in the discussion section of this study, could be implemented to establish if these could prove useful and cost-effective in improving outcomes & recovery in the TKR group.

CHAPTER 8. SUMMARY OF RESULTS AND CONCLUSIONS

The primary aim of this study was to investigate the effects of immobilisation and reduced weight-bearing on leg fracture and knee replacement patients, in order to quantify bone and muscle loss and to monitor recovery over a one year period. A postmenopausal population was chosen because they are already losing bone density systemically, are at an already increased fracture risk and may be at greater risk of further bone loss following immobilisation. The original aim of the study was to assess differences at baseline and over the course of twelve months recovery between four groups; controls, total knee replacement patients, patients with new leg fractures treated with internal fixation and those treated with plaster of Paris only. Due to difficulties with recruitment, an additional group was added as a cross-sectional arm to the study; these participants had sustained leg fractures more than one year previously but within the previous ten years. Factors including activity, function, weight-bearing, pain, treatments, therapies, health perceptions and mental wellbeing, that potentially contribute to bone loss and recovery, were also investigated. The primary goal was to provide information relating to increased future hip fracture risk that may lead to treatment options to alleviate bone loss and improve physical and functional recovery in these groups. The final groups recruited to the study and included in the analysis were: 43 controls, 19 total knee replacement patients (TKR), 9 newly fractured patients (#<3wks) and 24 patients with longstanding leg fracture (#>1yr).

Key findings

The main results from the study demonstrated that there were notable differences between the groups at baseline and in the progress of their recovery over the course of

the twelve month follow-up. It was evident that a complex interaction of numerous factors contributed to loss and recovery of bone and muscle mass, alongside functional and emotional recovery. The effects of poor function and depression, whilst debilitating in their own right, also have potential to exacerbate the bone and muscle loss, which results from reduced mechanical loading due to immobilisation. Bone loss at the hip, and muscle atrophy, following leg injury or surgery has implications for increased risk of hip fracture particularly for participants with pre-existing low hip BMD at the time of their injury or surgery.

Results - Controls

The control group demonstrated consistency throughout the study in all parameters under investigation providing a meaningful contrast to the remaining groups, and although some age related bone loss was expected over the one year period in this postmenopausal control population, few statistically or clinically significant changes occurred from baseline in either bone or body composition parameters.

Results - TKR

The results indicate that recovery following TKR surgery was slow and incomplete one year after the event. The effects of immobilization following surgery in this group were an immediate and statistically significant loss of ipsilateral bone mass at the total hip and at the NOF (after 6 months), accompanied by significant bilateral muscle atrophy that continued gradually over the following 6 months and remained one year after surgery. The clinical significance of these reductions in hip BMD are an increased risk of hip fracture that may be exacerbated by muscle loss/weakness that could affect patients' gait and postural stability thereby increasing the risk of falls. The TKR group

had relatively high mean hip BMD at baseline, probably resulting from general obesity levels in this group, and the reductions in BMD in absolute terms may not represent a major increase in fracture risk for the average patient. However, these data support the increased hip fracture rate reported in the year following TKR, and those patients at higher risk of hip fracture at baseline may require consideration for bone-sparing therapy to reduce their risk. Although the mean reduction in bone mass was relatively small in absolute terms for the average TKR participant, a correlation was found whereby participants with the lowest bone density at baseline lost more absolute BMD than those with high BMD. An exponential relationship exists between BMD and fracture risk which means that an equivalent absolute reduction in bone mass in participants with low BMD values, causes a greater increase in fracture risk than for a participant with higher BMD. Any bone loss may therefore present a substantial increase in hip fracture risk for participants with pre-existing low hip BMD, further supporting the requirement for baseline monitoring and therapeutic intervention for at-risk patients. Despite showing an overall improvement in most areas of function and activity over the twelve month duration of the study, the TKRs nonetheless failed to achieve the levels of the control group one year post surgery. TKR patients experienced the worst levels of depression and anxiety amongst the groups with the poorest recovery over the study period. Depression in this group mostly related to pain, anxiety, poor perceptions of health and a higher number of co-morbidities. Poor sleep was a key factor for depression in all of the groups but was not significantly related to pain.

Results – Fracture patients

The newly fractured patients (#<3weeks) were significantly different to the controls at baseline in a number of key functional areas that were the inevitable consequence of the

immobilization caused by their injury. The consequence of immobilization following leg fracture in the #<3wk group, was an immediate and statistically significant loss of ipsilateral bone mass at the total hip. These immediate bone losses were subsequently followed by recovery, returning to baseline values, or above, at the end of one year. Although the mean reduction in bone mass was relatively small for this group in absolute terms, as with the TKR group, a correlation was found whereby participants with the lowest bone density at baseline, lost more absolute BMD than those with high BMD such that, due to the exponential relationship which exists between BMD and fracture risk, those participants with pre-existing low BMD are potentially at a substantially heightened risk of hip fracture risk following bone loss. However, after an initial deterioration in hip BMD and general function, the newly fractured group demonstrated good recovery in physical and functional parameters, returning to levels comparable to the controls at the end of the study.

The #>1year group exhibited distinct differences to both the controls and the #<3wk group, differing from the other groups at baseline in significantly higher levels of bone sparing pharmacological treatments. This group scored significantly below the control group in almost all key outcomes suggesting that a long-term impairment in function and bone health may persist following injury. They demonstrated a long-term deficit in hip bone density on the ipsilateral side, which together with reduced levels of function and activity that inhibit restoration of BMD, may represent a heightened risk for future hip fracture. It is not possible to state that these impairments were attributable to the consequences of the fracture but as these participants presented as a distinct group compared to the controls and the #<3weeks group, the reasons for the differences they exhibit may merit further investigation. Despite the evident good recovery in the newly

fractured group at the end of the one year study period, participants from the cross-sectional arm of the study showed distinctly different results with a relatively high level of depression associated with anxiety and a previous history of more falls. The reasons for the apparent discrepancies between the two fracture groups are not clear but may be a consequence aberrant results due to the small number of participants in the #<3weeks group. They may also be potentially attributable to selection bias and the Hawthorne effect whereby behaviour may have been modified in the newly fractured participants, artificially optimising their recovery. The results from the #<3wk group are possibly therefore less representative of typical leg fracture patients than the #>1year group. A further longitudinal study across multiple centers to recruit sufficient participants is required to investigate this further.

With regard to depression, the newly fractured patients recovered well after an initial period of poor scores following their injury. The #<3wks group demonstrated worsening depression with lower pedometer scores at visit 1 and with reduced function scores at visit 2 suggesting that their depression was significantly related to their inability to perform their normal activities early on in their recovery. An interesting association emerged from the multiple regression analysis between depression and previous experience of falls in both the #<3wk and #>1yr groups that may involve a complex relationship between depression, poor physical function and fear of falling (265). Both the newly fractured group and the longstanding fracture groups had a history of previous fracture rates higher than the controls.

Implications

It is important to state that for the majority of women, loss of BMD at the hip following injury or surgery will present a very minimal increase in hip fracture risk. Whilst bone loss at the hip has been shown to be statistically significant in both the TKR and newly fractured groups, in a clinical context, the changes demonstrated for the average patients in this study are relatively small. Nevertheless the study sample is above average in densitometry terms compared with the NHANES database and is not therefore representative of the general population where mean BMD values would be lower. It is possible therefore that the results from this study underestimate the impact of post-fracture or post-surgical bone loss in the wider population. Although the group means for BMD at the hip sites were relatively high in the TKR and #<3wk groups, a proportion of each group had BMD scores in the osteopenic and osteoporotic range, indeed nine additional participants in these groups (4 and 5 participants respectively) were put onto bone sparing treatments as a consequence of reporting their densitometry results from the study. Epidemiological evidence has demonstrated a significantly increased hip fracture incidence in the year following TKR surgery (210, 211) and it is possible that apparently minor BMD changes in some patients in the lower BMD range could, in part, account for this. However, it is not known from these papers whether post-surgical hip fractures occurred on the ipsi- or contralateral sides and information in this regard would help to ascertain whether changes in ipsilateral bone density potentially contribute to this increased hip fracture risk alongside other factors such as muscle loss/weakness, impaired gait and an increased propensity for falls.

A further factor that may be of relevance in contributing to future fracture risk is obesity. The relationship between fracture risk and obesity is currently unclear and appears to be site-dependent. Past research has shown an association of obesity with higher rates of ankle and leg fracture in postmenopausal women (269) and it is also known to be the primary risk factor for knee OA: indeed the TKR group in this study was distinct in their high mean BMI relative to the other groups. Leg, particularly ankle, fractures are common in incidence in postmenopausal women (270) and TKR operations are increasing in frequency, doubling in the United States from 1999 to 2008 (281). Both leg fracture and OA are associated with increased age (255, 270) and as populations increase in longevity and the incidence of obesity and osteoarthritis rises, the prevalence of leg fractures and TKR procedures is likely to rise in the future. As the incidence of both conditions/procedures is high, a small increase in hip fracture risk resulting from either, could translate into large numbers of individuals ultimately affected by hip fracture with concomitant personal distress and financial costs to healthcare providers.

Results from the multiple regression analysis demonstrated that bisphosphonate use was the best overall predictor for change in BMD at the total hip, having a mitigating effect on bone loss. This suggests that prophylactic treatment may benefit patients at the highest risk of hip fracture. Currently there is no routine clinical pathway for DXA screening before surgery for TKRs or immediately following leg fracture and this would be valuable to identify patients at the greatest risk for bone loss and to assess the need for treatment. Interestingly, bisphosphonate use in TKR patients has also been shown to improve implant survival time after primary knee arthroplasty and to reduce revision rates; treatment may therefore confer an additional benefit to these patients beyond

fracture prevention (282). Relative to the financial cost of TKR surgery and the potential costs of subsequent hip fracture, screening and appropriate treatment could be a valuable and cost effective precaution.

Multiple regression analysis presented a mixed selection of variables that significantly influenced function (LEFS) in the different groups and at different stages of the study. Pain was the most frequently occurring explanatory variable causing a reduction in function as pain increased in all groups. In addition, less co-morbidity, lower age, higher health perception and increased pedometer activity all contributed to improved function amongst the groups. These results suggest that more appropriate or alternative methods for pain relief and an improved regime of physiotherapy and exercise, could potentially benefit patients and mitigate the long-term functional impairments demonstrated in the TKR and #>1year groups. As the #>1yr and the TKR groups had higher BMI than the controls, in the overweight and obese categories respectively, both might benefit from exercise regimes to improve function and activity generally, and also encourage weight loss to reduce impact forces on the legs.

Depression levels were demonstrated to be higher in the patient groups than in controls and this difference continued throughout the study for the TKRs and was also evident as a persistent factor in the longstanding fracture group. Depression and anxiety, above the thresholds for clinical levels, was also highest in these two groups. A significant association was demonstrated between depression and bone loss in the #<3wks group supporting findings from previous studies which show an association of depression with reduced BMD and increased fracture risk (101, 105, 279). In addition to the impact of depression on patients' quality of life, the association with bone loss may have implications for the treatment of depression in patients following fracture or surgery.

Nevertheless, caution may need to be applied as the use of pharmaceutical antidepressants is also associated with reduced BMD which could exacerbate fracture risk in patients already at risk of bone loss as a consequence of their injury. For newly fractured patients, there is little that can be changed in the early stages to improve their functional recovery during the process of fracture healing and reduced weight-bearing, therefore the inevitable frustrations of limited function and activity are unavoidable. As pain does not appear to contribute significantly to depression in this group and most participants are well medicated following injury, there may be limited potential to improve the experience for these patients other than possibly offering some aids to sleep. Results from the multiple regression analysis indicated that depression in the TKR group was significantly associated with pain, poor perceptions of health, and anxiety. A formal assessment for these conditions is indicated whereby patients could benefit from advice or counseling to alleviate their symptoms and potentially improve functional recovery. As the potential for anti-depressant drugs to exacerbate bone loss is a subject of ongoing research, the use of these treatments in this group should be considered with caution.

Previous studies have shown that rates of recovery of bone mass are slower than the original rate of bone loss, and return to customary levels of bone loading may not be sufficient to restore original bone density (9, 11). Heightened levels of exercise and activity, above habitual levels, may be required to stimulate recovery. It has been demonstrated in this study that the TKR group, whilst showing improved levels of function and activity over the study period, do not achieve the levels of the other groups one year post surgery. It may therefore take a considerable period of time and physical effort to achieve full recovery in this group. Although there is pre- and post-surgical

service provision for TKR patients in the form of advice, physiotherapy and supervised exercise classes, the interventions offered to individuals (in the setting of this study) were very inconsistent. Group exercise classes could be a cost-effective option for healthcare services, benefiting both TKR and fracture patients by improving their function and activity levels whilst also encouraging weight loss. As some association has been shown between bone loss and depression, social networks forged through these groups could afford peer support to aid mental wellbeing and may help patients to have more realistic expectations for their progress in recovery. As use of antidepressant drugs is also thought to be associated with bone loss, opportunities for peer support or counseling, to avoid the need for pharmaceutical interventions, might also prove valuable in prevention of future hip fractures in these patients.

Limitations

The study had several limitations, most notably the difficulties involved with recruitment and the potential for recruitment bias. There may also have been some recruitment bias with the TKRs. The study had a largely rural catchment area and as many participants were required to travel large distances to attend the data collection sessions at a time when they were prohibited from driving, only those patients with appropriate support were able to take part. This suggests that many of them enjoyed a level of social support that may have influenced their general state of wellbeing such that the study results could have underestimated the levels of depression and anxiety in a wider population. The sample used in this study was 100% of white Caucasian ethnicity coming from a relatively affluent rural catchment area in the Southwest of England. The pedometer results suggest that the controls were a relatively active group for their age range and were frequently from backgrounds that afforded them the leisure

to take part in the study. Although the socio-economic status of participants was not investigated, many, particularly amongst the control group, appeared to have backgrounds of relative affluence and good education that are generally associated with healthier lifestyles. To be equivalent to the population used for the NHANES database, on which DXA diagnostics are based, control participants would exhibit mean Z-scores of zero. However, the mean densitometry Z–scores at various sites were above average for all groups except the #>1yr group, indicating that participants from this region may not be fully representative of the national population which potentially limits the generalisability of the results. It cannot be ruled out that that the control group, due to selection bias, are substantially above average fitness and that the #>1year group are possibly more representative of the general population. A further limitation was the size of the #< 3 wks group. Due to recruitment difficulties, this group was smaller than anticipated and the analyses of results may be underpowered. Caution should therefore be used when interpreting results and this may account, in part, for the unexpected differences between this and the #>1yr group. In addition, because the #< 3 wks group was difficult to recruit, those subjects who did participate tended to have a keen interest in the research topic and it is feasible that they were susceptible to the Hawthorne effect, modifying their behaviour to optimize their recovery. It should also be acknowledged that a larger sample is more reliable for detecting significant associations in multiple regression, requiring increasing sample size for each additional predictor variable added to the model (271). It is therefore feasible that more of the independent variables would have been shown to have significant associations with the outcome variables had the sample size been larger. There were many potential and unavoidable confounders due to the nature of the pathologies under investigation, such as the presence of co-morbidities, previous knee replacements and treatments for low bone density that were prescribed

during the course of the study. Where appropriate and relevant to the outcome measures, these were added as explanatory variables in the analysis

Conclusion

Disuse bone loss in a post-menopausal population has not been previously reported, nor has it been investigated in a TKR population immediately following surgery. This study has demonstrated that bone loss at the hip, accompanied by muscle losses of varying degrees, is a consequence of immobilisation in both leg fracture and knee replacement patients. Bone loss, although a recognised consequence of immobilisation, is not currently investigated as a clinical outcome of leg fracture or surgery. For the majority of patients these changes will only result in a minimal increase in hip fracture risk, however epidemiological evidence has demonstrated an increase in hip fracture incidence post TKR surgery that suggests, for some patients with pre-existing low bone density, bone loss at the hip may make a contribution to this enhanced fracture incidence. As the number of patients undergoing TKR procedures increases globally, this may have a substantial impact on the incidence of hip fracture and the financial costs to health care providers. In addition to the physical effects of leg fracture or TKR, poor outcomes in function, activity and mental wellbeing contribute to a reduced quality of life that could potentially be improved for these patients.

It is important to acknowledge the limitations of imaging technologies and of the fracture risk assessment tools currently available for clinical use. Clinicians should be aware of the potential over-reliance on BMD and the limited range of risk factors in fracture assessment tools to predict fracture in the individual. An awareness of the potential complication of bone loss following immobilisation is required with

consideration of screening and prophylactic treatments, post injury/surgery, to avoid or alleviate bone loss, particularly where other risk factors for low bone density are present. Development of alternative or complementary technologies (including molecular imaging) and software tools to assess bone architecture should be welcomed and advancements in this area may improve clinicians' ability to predict fracture risk in the individual patient in the future.

Future work

As the recently fractured group used in this study was small and may have been influenced by selection bias, further work would be valuable to assess bone and muscle loss in a larger sample to confirm the validity of the results. It would be desirable to follow up the current cohort of participants at a later stage, of three to five years post baseline, to investigate longer-term changes in BMD and any hip fracture incidence. A large multi-center study is needed to investigate baseline DXA measurements in a wider TKR population and the extent of bone loss at one year post surgery.

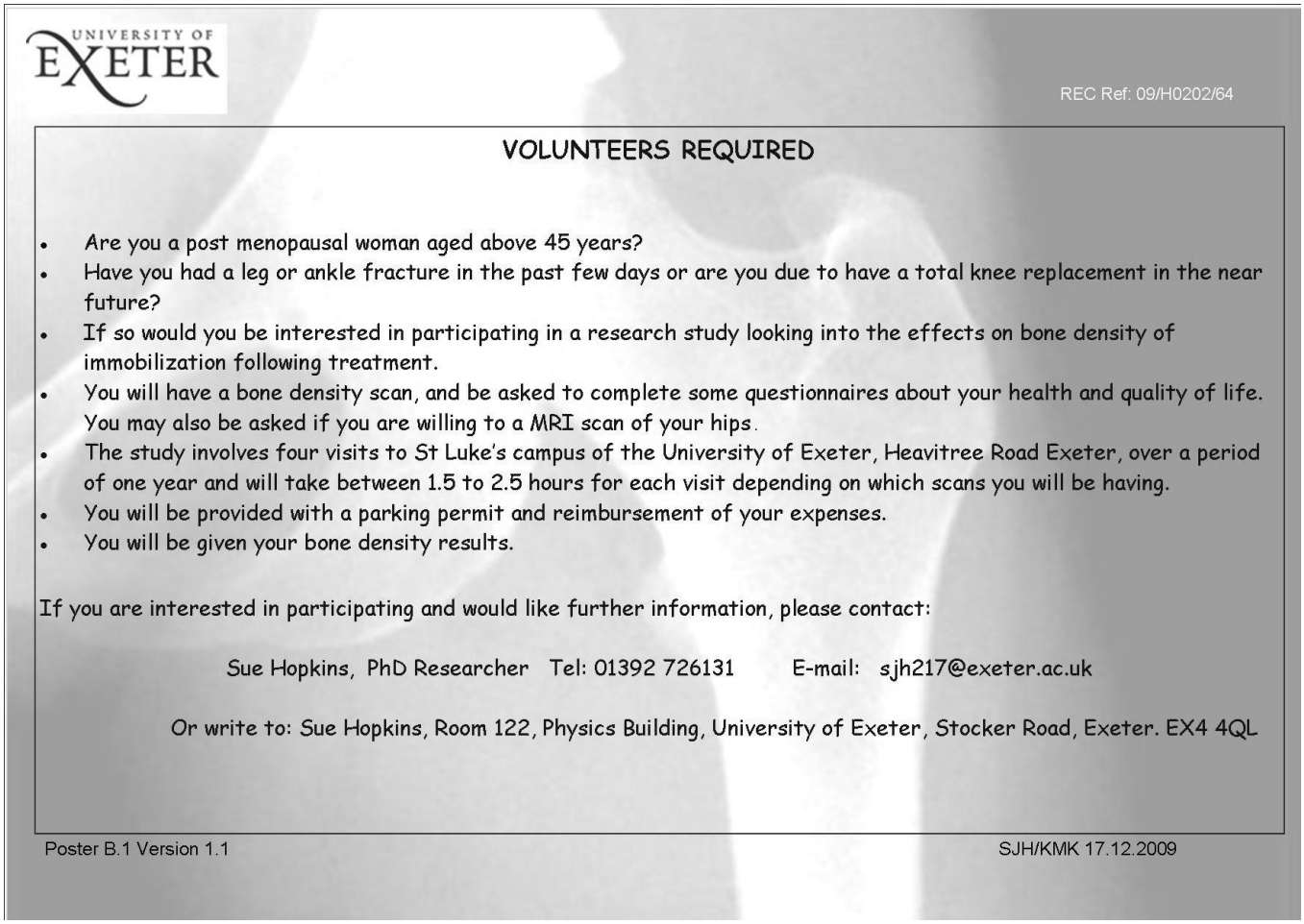
This study has only provided a fairly superficial overview of the prevalence of depression and anxiety in these participant groups and a more 'in depth' assessment of the causes of these conditions would be valuable. It would be particularly interesting to establish the reasons for high levels of depression in the #>1yr group and whether these are attributable in any way to the outcomes of their leg fracture.

Further work would be valuable to investigate the clinical- and cost-effectiveness of DXA assessment in the work-up pre-TKR to identify those patients at a higher fracture risk, and also whether implementation of improved pain relief and more consistently

applied post-surgical exercise regimes, including group classes, could prove beneficial and cost-effective in improving outcomes and recovery in the patient groups.

Appendix 1

Recruitment poster – patient groups



Appendix 2

Recruitment leaflet – Patient groups.

- You will have a bone density scan, and be asked to complete some questionnaires about your health and quality of life.
- You may also be asked if you are willing to have a MRI scan of your hips. Each visit will take approximately 1.5 hours or up to 2.5 hours if you also have a MRI scan.
- You and your doctor will be given your bone density results
- Please note that you may not be suitable to participate if you have had your fracture repaired by an external fixation device.

If you are interested in participating and would like further information, please contact:

Sue Hopkins
PhD Researcher

Tel: 01392 726131

E-mail:
sjh217@exeter.ac.uk

Or write to:
Sue Hopkins
Room 122
Physics Building
University of Exeter
Stocker Road
EX4 4QL

Leaflet B.1
V 1.0 SJH 03.11.2009

UNIVERSITY OF EXETER

VOLUNTEERS REQUIRED

Are you a post menopausal woman aged above 45 years?

Have you suffered a fracture of your lower leg in the past few days or are you due to have a total knee replacement in the near future?

If so would you be interested in participating in a research study looking into bone density?

What is the study about?

This is an important study which aims to investigate the effects on bone structure and density at the hip resulting from immobilization following treatment for fracture (broken bone) or total knee replacement.

It includes groups of control participants, lower limb fracture participants and participants undergoing total knee replacement.

Who is taking part?

We need 200 post menopausal (i.e. not having had a period for over 12 months) female volunteers, aged 45 years and older.

50 of these subjects will be controls who have not had lower limb fractures or total knee replacements. The remainder will be patients who have undergone immobilization following fracture of the lower limb or total knee replacement.

- The study involves three visits for control participants, or four visits for patient groups, to St Luke's campus of the University of Exeter, Heavitree Road, Exeter, over a period of one year.
- You will be provided with a parking permit and reimbursement of your expenses.
- If you have difficulty walking initially following your treatment, we can arrange a reserved parking space for you and a wheel chair escort from your car to the scanner.

Appendix 3

Disuse Osteopenia, short- and long-term effects

INFORMATION SHEET

Participant No: _____ Participant Initials:_____

Invitation:

You are being invited to take part in this research study. Before you decide it is very important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything which is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

Disuse osteopenia or osteoporosis, i.e. loss of bone density and strength, is a recognised complication of immobilization (restricted movement) and may occur as a result of inactivity following a leg or ankle fracture (break) or possibly after total knee replacement. The aim of this study is to investigate the severity and extent of any bone loss that results from immobilization following lower limb fracture or total knee replacement. The long-term goal is to identify risk factors, resulting from immobilisation, which may increase the likelihood of future fractures at the hip. This will help to identify when and to whom preventative treatments should be administered to reduce any bone density loss.

Why have I been chosen?

We are approaching women who have gone through the menopause (i.e. not had a period for over 12 months) and undergone immobilization following leg or ankle fracture or total knee replacement. The study will include fracture patients who have had bone repairing surgery using plates and screws and also patients whose fractures have only been treated by plaster cast. It will not include patients whose fractures have been repaired by metal work fixed to the outside of their leg. We also wish to recruit non-patients (controls) who have not undergone injury or surgery to their leg.

You have been asked to participate as you fit into one of these groups. Thank you for showing an interest in this project. This sheet is an invitation for you to take part in our project. It will tell you a bit more about the project and what we would like you to do. Please read this carefully before deciding whether or not to take part. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you of any kind and we thank you for considering our request.

What is the project about?

This study is looking at factors that may increase bone loss following leg or ankle injury/surgery and may therefore also increase the future risk of hip fracture. The end goal is to be able to identify those who may be at an increased risk of bone loss and potential increased risk of hip fracture and identifying potential preventative treatments.

Who is taking part?

We need 200 post-menopausal female volunteers, aged 45 years and older. 50 of these subjects will be non–patients (controls) who have not had lower limb fractures or total knee replacements. The remainder

will be patients who have undergone immobilization following fracture of the leg/ankle or total knee replacement.

What will I be asked to do?

If you volunteer for this project we will ask you to visit us at the University of Exeter on up to four occasions at intervals of 6 weeks, 6 months and 1 year following an initial assessment. The initial assessment will take place before surgery for total knee replacement or 2 weeks after treatment for lower limb fractures. Control subjects will only be asked to visit 3 times for the initial assessment, and at intervals of 6 months and 1 year. During your first visit we will help you to fill in some questionnaires about your health and any risk factors you may have for osteoporosis. Each visit may last for approximately 1.5 hours or up to about 2.5 hours if you are also selected for an MRI scan. Each visit will involve;

Height and weight measurements which will take about 5 minutes.

A DXA scan of the bones of your spine, hip and whole body to measure the strength of your bones. For these scans you lay on your back on the scanner, which is of a very open design. These scans use x-rays but of a very low dose. The same as if you were to sit outside in the Exeter sun for ½ a day, or less than taking a transatlantic flight. These scans will take about 30 minutes. It is possible that you will be diagnosed as having low bone density or osteoporosis from these scans. If this is the case, your GP will be informed and you will be advised to make an appointment to see him or her.

Some participants may also be asked to have a Magnetic Resonance Imaging (MRI) scan of the hips. This is entirely optional and you need not participate if you do not wish to. It is also subject to scanner availability. The MRI scanner uses a strong magnetic field and does not use X-rays or ionising radiation, which means there is no radiation dose associated with these scans. During these scans you will lay on your back inside the scanner. Most participants are able to enter the scanner feet first with their head remaining outside of the scanner ring. However it is sometimes necessary for taller people (above 6 foot) to enter head first. We will take a number of images, which will take approximately 45 minutes. You will not feel any unusual sensations from the magnet. There are loud (clunking) noises like the banging radiators make in houses that have steam/hot water heating systems. You will be able to see and talk to the operators and you can also bring a CD of your favourite music to listen to during your scan. You will be required to complete a safety questionnaire before this scan which will tell us if you are able to have the scan. If you have ever had metal fragments in your eyes or have a pacemaker, you will not be able to have the MRI part of the study.

For limited periods during the study, you will be asked to wear a small unobtrusive piece of equipment called an activity monitor/pedometer to measure your physical activity. You will also be asked to fill in a questionnaire about the types, duration and intensity of your physical activity during the same period as the accelerometer measurements.

When you are allowed to weight-bear, we will assess your ability to do so by using a questionnaire and a testing device called force plates (similar to bathroom scales) during your visits. We will also ask you to fill in some questionnaires about your quality of life, wellbeing and functional improvement during your recovery.

We fully appreciate that you may have difficulty walking initially following you treatment and, if required, we can arrange a reserved parking space for you and a wheel chair escort from your car to the scanner.

Can I change my mind?

You can stop being in the project at any time without giving a reason and without any disadvantage to yourself of any kind.

What will you do with the information?

We will collect your name, address and contact details and information about any relevant clinical conditions, medication and personal data such as date of birth, weight, blood results etc and the data generated from the tests. We will store them in the study files and on a computer. The files will be protected in a locked room with only research team having access. The computers are protected with passwords. The building which houses all the research data is security protected. When the data is in store the name and addresses will be removed from the data so that it can be identified only by an ID code and the data will be stored for 15 years. When the results of the study are analysed individual participants will not be identifiable. The data will be accessed and analysed only by the departments' research staff, the supervisors of the research and research auditors. You are welcome to request a copy of the results of the project.

With your consent, results that may be of use to your doctor will be sent to your GP. If you are under the care of a consultant, they will also be advised. Confidentiality may not be breached without your consent unless for any reason there is a significant risk of harm to yourself.

What if I have any questions?

If you have any questions at any time, please feel free to ask Sue Hopkins on 01392 726131 or E-mail sjh217@exeter.ac.uk. If you wish to talk to someone who is independent of the study team, please contact Rachel Palfrey on 01392 264086.

What do I do if I have any worries of complaints?

If you feel your treatment either prior to the study, during or after the study is of concern to you in any way, please contact Dr Karen Knapp on 01392 264133 or Dr, Joanne Welsman on 01392 262882.

What do I do next?
If you have read and understood everything that we want you to do and are happy to take part, please return the enclosed **contact details form** so that we can assess your suitability to participate. Please also sign the attached consent form and retain it for your own record. You will be asked to sign another copy for our use when you attend your first appointment.

Sue Hopkins
PhD Researcher

This project has been reviewed and approved by the Local Research Ethics Committee.

Appendix 3

Disuse Osteopenia, short- and long-term effects.

CONSENT FORM FOR PARTICIPANTS

I have read the information sheet concerning this project and understand what it is about. All my questions have been answered to my satisfaction. I understand that; (please initial each box)

- My participation in the project is entirely voluntary. ☐
- I am free to withdraw from the project at any time without having to give a reason and without any disadvantage. ☐
- The results of the project may be published but my anonymity will be preserved. ☐
- I will be asked to complete questionnaires about my health and risk factors for osteoporosis. ☐
- I will be asked to complete questionnaires about my healing, wellbeing, physical activity, functional progress and quality of life. ☐
- I will have my ability to weight-bear assessed using a questionnaire and force plates. ☐
- My height and weight will be measured. ☐
- I will have scans of the hip, spine and whole body to look at bone strength. These scans involve a small dose of x-rays which is the same as spending ½ day outside in the Exeter sun. ☐
- If asked, I will have a MRI scan of my hips to look at bone structure at this site. ☐
- I will wear an activity monitor/pedometer to measure my physical activity for limited periods during the study. ☐
- I agree to take part in this project. ☐
- I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

Signed (Date)
Participant…….. ……..……

Signed (Date)
Researcher…….. ……..…….....

This project has been reviewed and approved by the Local Research Ethics Committee.

Appendix 4

Invitation to participate in study – patient groups

Royal Devon and Exeter NHS Foundation Trust

DATE

Ms. XXXXXX

Dear Ms XXXXX,

Re: Disuse Osteopenia, short- and long-term effects.

I am writing to you regarding the above study to invite you to participate either as a leg or ankle fracture (broken bone) or total knee replacement patient. This is an important study which aims to investigate the effects on bone structure and density at the hip resulting from immobilization (restricted movement) following treatment for fracture or total knee replacement. It includes groups of non-patient participants, leg and ankle fracture participants and participants undergoing total knee replacement.

Please find enclosed a participant information sheet telling you more about the study. You are under no obligation to participate in this study and your treatment at the hospital will not be affected by your decision.

The study requires four visits to the University of Exeter, St Luke's campus, which may take up to 1.5 hours for each visit or 2.5 hours if you are also having an MRI scan. You will be provided with a parking permit and reimbursement of your expenses.

If you would like to take part, please return the 'Contact details' form enclosed. If you have any questions and wish to discuss the study further, do not hesitate to contact the research study co-ordinator, Sue Hopkins on 01392 726131 or e-mail sjh217@exeter.ac.uk. Please note that this phone line is not manned full time and we would be grateful if you could leave a message with your name, telephone number and some convenient times to return your call.

If you have sustained a fracture, it is important that we undertake the first scans around two weeks after your treatment and therefore we would be very grateful if you could reply as soon as possible. If you are going to have a total knee replacement, we will need to perform the first scans before your operation.

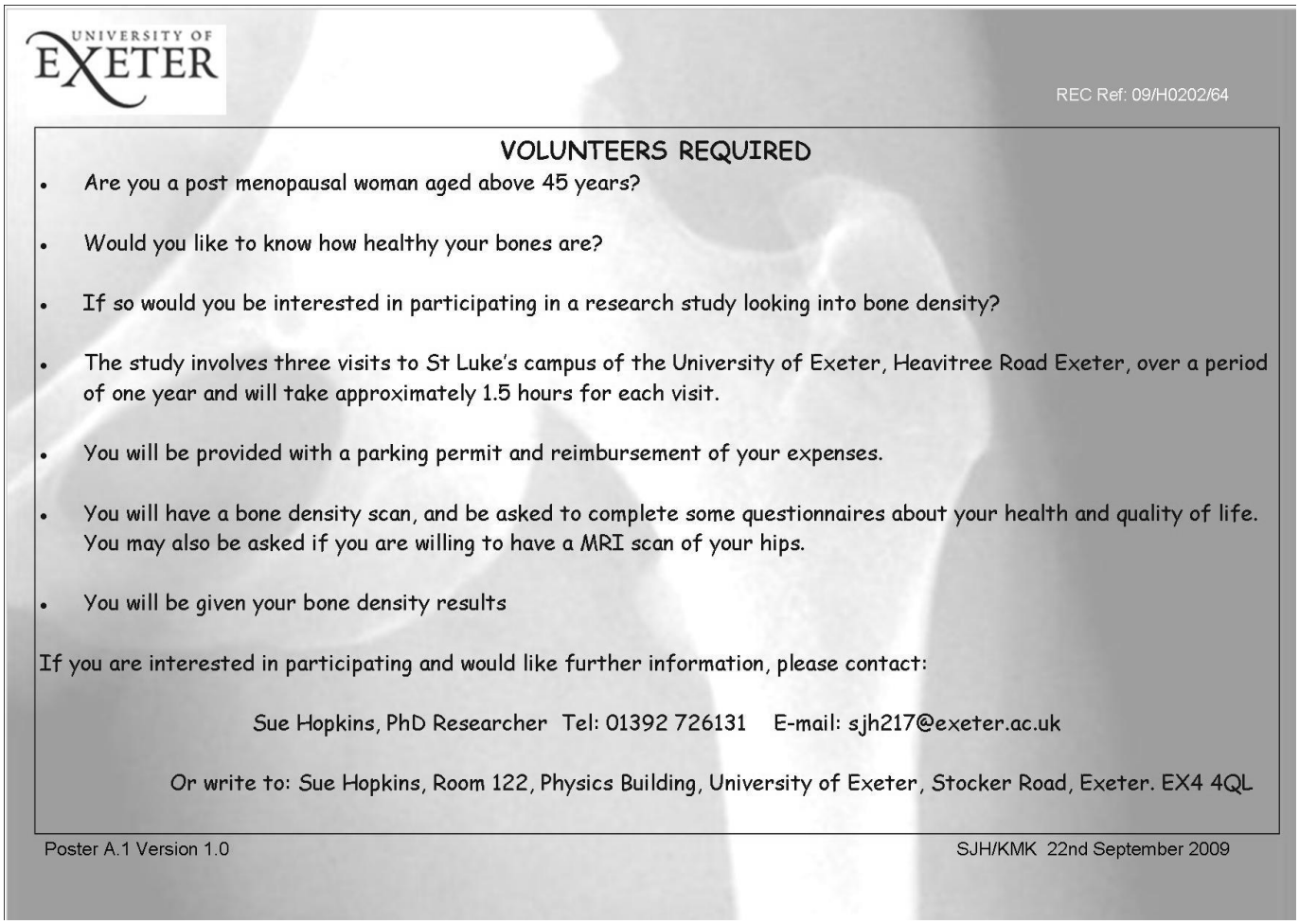
Thank you for considering our request.
Yours sincerely

pp. Mr. [redacted]
Consultant Orthopaedic Surgeon
Royal Devon & Exeter NHS Foundation Trust

Chairman: [redacted] **Chief Executive:** [redacted]

Appendix 5

Recruitment poster - Controls



Appendix 6

Recruitment leaflet - Controls

Please note that you may not be suitable if:

You have had a leg or ankle fracture or total knee replacement after the age of 21 years.

You have been immobilised (not able to walk or stand) for more than 4 weeks within the last 10 years or since you have had the menopause.

You have osteoarthritis likely to result in a knee replacement in the next year.

You have been taking corticosteroids above 2.5 g for more than 3 months within the last 5 years.

If you are interested in participating and would like further information, please contact:

Sue Hopkins
PhD Researcher

Tel: 01392 726131

E-mail:
sjh217@exeter.ac.uk

Or write to:
Sue Hopkins
Room 122
Physics Building
University of Exeter
Stocker Road
EX4 4QL

Leaflet A.1
V 1.1 SJH 17.12.2009

UNIVERSITY OF EXETER

VOLUNTEERS REQUIRED

Are you a post menopausal woman aged above 45 years?

Would you like to know how healthy your bones are?

If so would you be interested in participating in a research study looking into bone density?

What is the study about?

This is an important study which aims to investigate the effects on bone structure and density at the hip resulting from immobilization following treatment for fracture (broken bone) or total knee replacement.

It includes groups of control participants, lower limb fracture participants and participants undergoing total knee replacement.

Who is taking part?

We need 200 post menopausal (i.e. not having had a period for over 12 months) female volunteers, aged 45 years and older.

50 of these subjects will be controls who have not had lower limb fractures or total knee replacements. The remainder will be patients who have undergone immobilization following fracture of the lower limb or total knee replacement.

- The study involves three visits for control participants, or four visits for patient groups, to St Luke's campus of the University of Exeter, Heavitree Road, Exeter, over a period of one year.
- You will be provided with a parking permit and reimbursement of your expenses. You will have a bone density scan, and be asked to complete some questionnaires about your health and quality of life.
- You may also be asked if you are willing to have a MRI scan of your hips. Each visit will take approximately 1.5 hours or up to 2.5 hours if you also have a MRI scan.
- You will be given your bone density results

Appendix 7

Recruitment poster – Fracture > 1 year group

Appendix 8

Recruitment leaflet – Fracture > 1 year group

- Your visit will take approximately 1.5 hours or up to 2.5 hours if you also have a MRI scan.
- You and your doctor will be given your bone density results

Please note that you may not be suitable if:

You have had a hip or knee replacement.

You have been immobilised for more than 4 weeks within the last 10 years or since you have had the menopause for reasons other than your leg/ankle fracture

You have been taking corticosteroids above 2.5 g for more than 3 months within the last 5 years.

If you are interested in participating and would like further information, please contact:

Sue Hopkins
PhD Researcher

Tel: 01392 726131

E-mail:
sjh217@exeter.ac.uk

Or write to:
Sue Hopkins
Room 122
Physics Building
University of Exeter
Stocker Road
EX4 4QL

Leaflet C
V 1.0 SJH 6.10.2010

UNIVERSITY OF EXETER

VOLUNTEERS REQUIRED

Are you a post menopausal woman aged above 45 years?

Have you had a leg or ankle fracture after the age of menopause and more than one year ago? Was it within the past 10 years and did it cause you to be unable to weight bear on that leg for around 6 weeks?

If so would you be interested in participating in a research study looking into bone density?

What is the study about?

This is an important study which aims to investigate the effects on bone structure and density at the hip resulting from immobilization following treatment for fracture (broken bone) or total knee replacement.

It includes groups of control participants, participants with previous leg & ankle fractures, new fracture participants and participants undergoing total knee replacement.

Who is taking part?

We need a total of 200 post menopausal (i.e. not having had a period for over 12 months) female volunteers, aged 45 years and older.

Of these, 50 will be participants who have had a leg or ankle fracture after the age of menopause and within the past 10 years that caused them to be unable to weight bear on that leg for around 6 weeks?

Do you fit this category and would you be interested in taking part?

- The study involves one visit to St Luke's campus of the University of Exeter, Heavitree Road, Exeter.
- You will be provided with a parking permit and reimbursement of your expenses.
- You will have a bone density scan, and be asked to complete some questionnaires about your health and quality of life.
- You may also be asked if you are willing to have a MRI scan of your hips. You do not need to have the MRI scan if you prefer not to.

Appendix 9

MRI Participant Safety Checklist

Name: **Date of Birth:**
Weight: **Name of Study/Volunteer Number:**

Please check the following list carefully, answering all appropriate questions. Please do not hesitate to ask staff, if you have any queries regarding these questions.

1. Do you have a pacemaker, artificial heart valve or coronary stent? Yes/No

2. Have you ever had major surgery? Yes/No
   If yes, please give brief details.

3. Do you have any aneurysm clips (clips put around blood vessels during surgery)? Yes/No

4. Do you have any implants in your body

   Yes ☐ No ☐ Joint replacements, pins or wires
   Yes ☐ No ☐ Implanted cardioverter defibrillator (ICD)
   Yes ☐ No ☐ Electronic implant or device
   Yes ☐ No ☐ Magnetically-activated implant or device
   Yes ☐ No ☐ Neurostimulation system
   Yes ☐ No ☐ Spinal cord stimulator
   Yes ☐ No ☐ Insulin or infusion pump
   Yes ☐ No ☐ Implanted drug infusion pump
   Yes ☐ No ☐ Internal electrodes or wires
   Yes ☐ No ☐ Bone growth/bone fusion stimulator
   Yes ☐ No ☐ Any type of prosthesis
   Yes ☐ No ☐ Heart valve prosthesis
   Yes ☐ No ☐ Eyelid spring or wire
   Yes ☐ No ☐ Metallic stent, filter or coil
   Yes ☐ No ☐ Shunt (spinal or intraventricular)
   Yes ☐ No ☐ Vascular access port and/or catheter
   Yes ☐ No ☐ Wire mesh implant
   Yes ☐ No ☐ Bone/joint pin, screw, nail, wire, plate etc.
   Yes ☐ No ☐ Other Implant_____

5. Do you have an artificial limb, calliper or surgical corset? Yes/No

6. Do you have any shrapnel or metal fragments, for example from working in a machine tool shop? Yes/No

7. Do you have a cochlear implant? Yes/No

8. Do you wear dentures, plate or a hearing aid? Yes/No

9. Are you wearing a skin patch (e.g. anti-smoking medication), have any tattoos, body piercing, permanent makeup or coloured contact lenses? Yes/No

10. Are you aware of any metal objects present within or about your body, other than those described above? Yes/No

11. Are you susceptible to claustrophobia? Yes/No

12. Do you suffer from blackout, diabetes, epilepsy or fits? Yes/No

For women:

13. Are you pregnant or experiencing a late menstrual period? Yes/No

14. Do you have an intra-uterine contraceptive device fitted? Yes/No

15. Are you taking any type of fertility medication or having fertility treatment? Yes/No

Important Instructions

Remove all metallic objects before entering the scanner room including hearing aids, mobile phones, keys, glasses, hair pins, jewellery, watches, safety pins, paperclips, credit cards, magnetic strip cards, coins, pens, pocket knives, nail clippers, steel-toed boots/shoes and all tools. Loose metallic objects are especially prohibited within the MR environment.
I have understood the above questions and have marked the answers correctly.

Signature (Participant/Parent/Guardian) Date

MR Centre Staff Signature

Appendix 10

Bone Questionnaire

Please bring the completed questionnaire with you for your first appointment.

If you have any difficulties filling in the form, you can discuss these with the researcher at your appointment.

Bone Questionnaire (Female)

Please complete **all** the appropriate sections, using the tick boxes where provided.

Date questionnaire completed
……

Surname ……..…….Forename(s)……Title..…….

Address ….……

……Postcode…...……..
.
Telephone Number (including area code) ……..……

Date of Birth …… (day/month/year) Age.....

Gender Female

Ethnic Background White [ ] Oriental [ ]
Black [ ] Mixed [ ]
Asian [ ] Other [ ]

Height …….. Weight
……..……...

Height at age 21…… Weight at age
21…….

GP Name ……..…….

GP Address ……..…….

……..…….

GP Telephone Number ……..…….

Have you had a DXA scan in the past 6 months? Yes [ ] No [ ]

If yes, where was this done? .....

……..

Medical History

1. Have you ever suffered from any of these conditions?

	No	Yes	Please state when diagnosed and duration of disease
Rheumatoid arthritis			
Osteoarthritis			
Ankylosing spondylitis			
Diabetes			
Overactive thyroid			
Underactive thyroid			
Breast cancer			
Other cancer			
Pagets disease of bone			
Liver disease			
Kidney disease			
Gastric surgery			
Lactose intolerance (milk allergy)			
Crohn's disease			
Coeliac disease			
Irritable bowel syndrome			
Malabsorption syndrome			
Osteomalacia (rickets)			
Bulimia			
Anorexia nervosa			

2. Do you suffer from any other on-going disease? Yes [ ] No [ ]

   If yes, please state disease and duration……..……

   ……..

3. Have any of your family (parents / brothers / sisters / children / aunts / uncles / nieces / nephews / grandparents) suffered from the following conditions?

   Broken hip, spine &/or wrist? Yes [ ] No [ ] Which relative?…….....…

   Other broken bones? Yes [ ] No [ ] Which relative?…….……..

   Osteoporosis? Yes [ ] No [ ] Which relative?…….……..

4. Do any other diseases run in your family? Yes [ ] No [ ]

If yes, please state the disease, and the relatives affected……...

……..……
…

5. Have you been immobilised for more than 6 wks (complete bed rest/. hospitalisation)? Yes [ ] No [ ]

If yes, was this before the age of 25 [ ], or after the age of 25 [ ]

6. Have you ever taken any of the following drugs?

Drug	No	Yes	For how long did you take them?
Corticosteroids **(Please state dose)**			
Anticonvulsants			
Diuretics			
Chemotherapy			
Immunosuppresive agents			
Heparin			
Thyroxine			
Didronel (Etidronate)			
Fosamax (Alendtronate)			
Calcitonin			
Actonel (Risidronate)			
Teriparatide (PTH)			
Protelos (Strontium Ranalate)			
Pamidronate (infusions)			
Zolendronate (injection)			
Ibandronate			
Fluoride			

7. Have you taken any other drugs fro greater than 6 months? Yes [ ] No [ ]

What drug?	For how Long?

8. Do you take any of the following dietary supplements?

Supplement	No	Yes	For how long
Multivitamins			
Calcium			
Vitamin D			
Other (please state)			

9. Have you ever fractured (broken) any bones? Yes [ ] No [ ]

If yes, please state how old you were, which bone(s) you broke, and how it happened, (please be as accurate and specific as possible):

Age	Bone	What Happened?

10. Do you, or have you in the past suffered from back pain? Yes [ ] No [ ]

If yes, how many episodes and how severe was the pain?.....

……

11. Have you had any falls in the last year? Yes [ ] No [ ]

If yes, now many and how did they happen?

Fall No	How did it happen	Did you sustain any injuries?

Lifestyle

12. Please tick which best applies to you

Current smoker	[ ]
Ex-smoker	[ ]
Never Smoked	[ ]

If ex-smoker, what age were you when you stopped? .....

How many cigarettes did you or do you smoke per day?.....……

How may years did you or have you smoked for? ……..……

13. How much alcohol do you drink per week?
(1 unit = ½ pint beer, a measure of spirits or a glass of wine)

Never	[ ]	11-15 units per week	[ ]
Social occasions only	[ ]	16-20 units per week	[ ]
1-5 units per week	[ ]	More than 20 units per week	[ ]
6-10 units per week	[ ]		

14. Are you vegetarian? Yes [ ] No [ ] If yes, for how long?.....…years

Are you vegan? Yes [ ] No [ ] If yes, for how long?.....…years

15. How many cups or cans of caffeine-containing beverages (coffee, tea and soft drinks such as cola) do you drink per day?

None	[ ]	11 – 15 cups/cans per day	[ ]
1 – 5 cups/cans per day	[ ]	More than 15 cups/cans per day	[ ]
6-10 cups/cans per day	[ ]		

16. How much time do you typically spend taking exercise (for example walking or cycling out of doors) each day?

None	[ ]
Some, but less than half an hour	[ ]
Half to one hour	[ ]
More than one hour	[ ]

17. Please outline any sporting or other activities you do partake in, and for how much time each week you spend doing these.

……

……

*The rest of the questionnaire is for completion by **women** only*

18. How old were you when your periods started?……..

Has there been any time when your periods have stopped for a time of more than 6 months except during pregnancy and menopause? Y[ ] N [ ]

If Yes, for how long did they stop?……

19. Have you had a hysterectomy? Yes [ ] No [ ]

If yes, at what age and for what reason? Age ……..

Reason……..

Have you had your ovaries removed?Yes [ ] No [ ] Don't know [ ]

If yes, was 1 ovary removed [ ] or both removed [ ] How old were you?

20. Are you still having natural periods? Yes [ ] No [ ]

If yes, are they regular? Yes [ ] No [ ]

If no and your periods stopped naturally, at what age did they stop?……..

21. Are you on, or have you ever taken HRT? Yes [ ] No [ ]

If yes, for how long have you taken it?……..

Are you still taking HRT? Yes [ ] No [ ]

If you have stopped taking HRT, why did you stop? ……..

……

22. Are you on, or have you ever taken the oral contraceptive pill? Y [ ] N [ ]

If yes, for how long have you taken it?…….

Are you still taking it? Yes [ ] No [ ]

23. How many children have you had?……

Did you breast feed your children? Yes [ ] No [ ]

If yes, for how many months did you breast feed each baby?

Baby	1	2	3	4	5
Months breast fed					

Appendix 11

The Lower Extremity Functional Scale

We are interested in knowing whether you are having any difficulty at all with the activities listed below **because of your lower limb problem** for which you are currently seeking attention. Please provide an answer for **each** activity.

Today, *do you* or *would you* have any difficulty at all with:

	Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
1	Any of your usual work, housework, or school activities.	0	1	2	3	4
2	Your usual hobbies, re creational or sporting activities.	0	1	2	3	4
3	Getting into or out of the bath.	0	1	2	3	4
4	Walking between rooms.	0	1	2	3	4
5	Putting on your shoes or socks.	0	1	2	3	4
6	Squatting.	0	1	2	3	4
7	Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
8	Performing light activities around your home.	0	1	2	3	4
9	Performing heavy activities around your home.	0	1	2	3	4
10	Getting into or out of a car.	0	1	2	3	4
11	Walking 2 blocks.	0	1	2	3	4
12	Walking a mile.	0	1	2	3	4
13	Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
14	Standing for 1 hour.	0	1	2	3	4
15	Sitting for 1 hour.	0	1	2	3	4
16	Running on even ground.	0	1	2	3	4
17	Running on uneven ground.	0	1	2	3	4
18	Making sharp turns while running fast.	0	1	2	3	4
19	Hopping.	0	1	2	3	4
20	Rolling over in bed.	0	1	2	3	4
	Column Totals:					

Minimum Level of Detectable Change (90% Confidence): 9 points SCORE: _____/ 80

Source: Binkley et al (1999): The Lower Extremity Functional Scale (LEFS): Scale development, measurement properties, and clinical application. Physical Therapy. 79:371-383.

Appendix 12

Quality of Life Questionnaire EQ-5D

Participant ID ..... Participant initials.....

Date.....

Is this your:
1st Appointment
6 week Appointment
6 month Appointment
12 month Appointment

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-Care
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

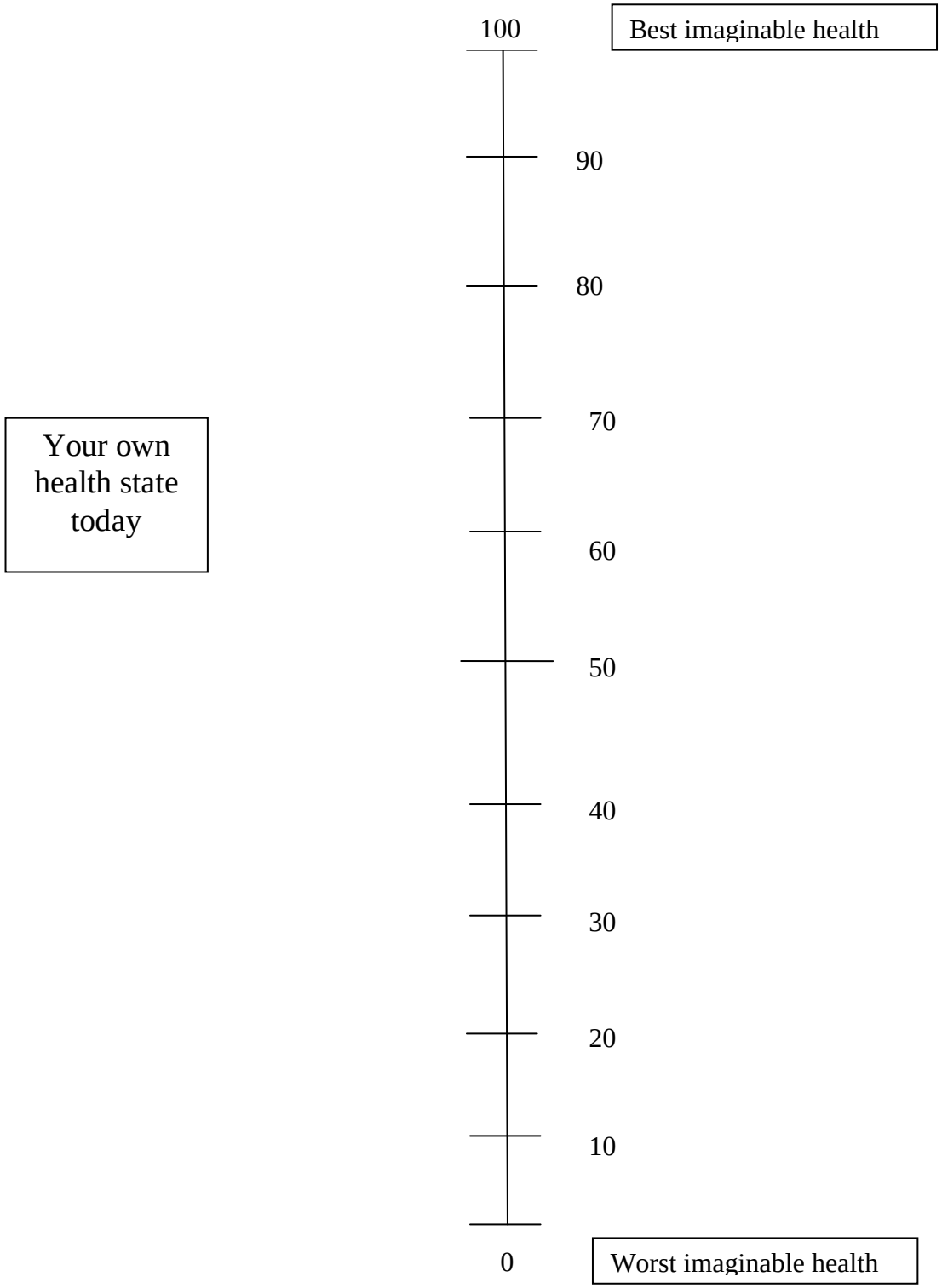
Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

Appendix 12

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



EQ-5D UK English version

Kajang Cheung [cheung@euroqol.org]

Sent: 30 November 2009 10:05

To: Hopkins, Susan

Attachments: UKenglishclin.doc (90 KB)

Dear Ms Hopkins,

Thank you for registering your research at the EuroQol Group's website.

As the study you registered at the EuroQol website involves low patient numbers and is not funded by a pharmaceutical company/medical device manufacturer, or any other profit-making stakeholders, you may use the EQ-5D instrument free of charge. If this is not the case, or the situation changes, please inform us as the EuroQol Group Foundation has a specific policy for large academic studies and/or studies funded by profit making bodies.

Please find attached the UK English version of the EQ-5D (word format). A brief user guide is downloadable from the homepage of the EuroQol website (www.euroqol.org)

Kind regards,

Kajang Cheung, MSc.
User Support Officer & Junior Researcher
EuroQol Executive Office
www.euroqol.org

What is EQ-5D?
EQ-5D versions
How to obtain EQ-5D
Valuation of EQ-5D
Population norms
Proceedings search
Reference search
EQ-5D publications
FAQs

FAQs

How long should the EQ VAS be?
Officially, for paper versions, the EQ VAS scale should be 20cms. All methodological and developmental work has been carried using this length. To ensure that you print the correct length, make sure your paper size is set at A4 and the box in your printing instructions labelled 'scale to paper size' is set at 'no scaling'.

Can I use only the EQ-5D descriptive system or only the EQ VAS?
We cannot advise this. EQ-5D is a 2-part instrument so if you only use 1 part you cannot claim to have used EQ-5D in your publications.

What is the difference between the EQ-5D descriptive system and the EQ VAS?
The descriptive system can be represented as a health state, e.g. health state 11212 represents a patient who indicates some problems on the usual activities and anxiety/depression dimensions. These health states can be converted to a single index value using (one of) the available EQ-5D value sets. These value sets have been derived using VAS or TTO valuation techniques, and reflect the opinion of the general population. The EQ VAS scores are patient-based and are therefore not representative of the general population. The EQ VAS self-rating records the respondent's own assessment of their health status. The EQ VAS scores however are anchored on 100 = best imaginable health and 0 = worst imaginable health, whereas the value sets are anchored on 11111 = 1 and dead = 0 and can therefore be used in QALY calculations.

What is the difference between the VAS and TTO techniques?
The difference between the value sets based on TTO and those based on VAS is that the techniques used for the elicitation of the values on which the models are based differ. In the TTO task, respondents are asked, for example, to imagine they live in a health state (e.g. 22222) for 10 years and then asked to specify the amount of time they are willing to give up to live in full health instead (i.e. 11111). For example, someone might find 8 years in 11111 equivalent to 10 years in 22222. The VAS technique on the other hand, asks people to indicate where, on a vertical thermometer-like scale ranging from best imaginable health to worst imaginable health, they think a health state should be positioned.

Can I publish our study using EQ-5D?
Yes, you are free to publish your results. If you are reproducing the EQ-5D in an appendix we request that you use the sample version of EQ-5D and that the following text is included in the footer: '© 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group'.

For what period of time does EQ-5D record health status?
Self-reported health status captured by EQ-5D relates to the respondent's situation at the time of completion. No attempt is made to summarise the recalled health status over the preceding days or weeks, although EQ-5D has been tested in recall mode. An early decision taken by the EuroQol Group determined that health status measurement ought to apply to the respondent's immediate situation - hence the focus on 'your own health state today'.

General population value sets vs patient population value sets
If you want to undertake a utility analysis you will need to use a value set. Generally speaking utility analysis requires a general population-based value set (as opposed to a patient-based set). The rationale behind this is that the values are supposed to reflect the preferences of local taxpayers and potential receivers of healthcare. Additionally, patients tend to rate their health states higher than the general population because of coping etc, often underestimating their need for healthcare. The EQ-5D value sets are therefore based on the values of the general population.

Multinational clinical trials
Information relating to EQ-5D health states gathered in the context of multinational trials may be converted into a single summary index using one of the available EQ-5D value sets. There are different options available to do this using appropriate value sets-however the choice depends on the context in which the information will be used by researchers or decision makers. In cases where data from an international trial are to be used to inform decision makers in a specific country, it seems reasonable to expect decision makers to be interested primarily in value sets that reflect the values for EQ-5D health states in that specific country. So for example, if applications for reimbursement of a drug are rolled out from country to country, country-specific value sets should be applied and reported in each pharmaco-economic report. This is no different from the requirement to use country-specific costs. In the absence of a country-specific value set, the researcher should select another set of values for a population that most closely approximates that country. Sometimes however, information about utilities is required to inform researchers or decision makers in an international context. In these instances, 1 value set applied over all EQ-5D health states data is probably more appropriate.

The decision about which value set to use will also depend on whether the relevant decision making body in each country specifies any requirements or preferences in regard to the methodology used in different contexts (e.g. TTO, standard gamble (SG), VAS or discrete choice modelling (DCM)). These guidelines are the topic of an international ongoing debate but the EuroQol Group website is planning to provide a summary of health care decision-making bodies internationally, and their stated requirements regarding the valuation of health states.

Detailed information regarding the valuation protocols, guidelines on which value set to use and tables of all available value sets has recently been published by Springer in: EuroQol Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide' (see section 8 for more information). Chapter 4 by Nancy Devlin and David Parkin will be of special interest to researchers pondering the issue of which value set to use.

Appendix 13

PHQ-9

PATIENT HEALTH QUESTIONNAIRE - 9				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the number of days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as watching television or reading	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
	FOR OFFICE CODING **___0__+_____+_____+_____** **=Total Score:_____**			

If you ticked any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc.

USER-AGREEMENT
EXISTING TRANSLATIONS

USE OF THE PATIENT HEALTH QUESTIONNAIRE (PHQ)

Date : _26 _03 _10
day month year

1. USER'S NAME

This user-agreement is between MAPI Research Trust (on behalf on Pfizer Inc.) and:

Name : ***Please have the information type written*** The University of Exeter("User")
Title : .....
Company :
Address : Northcote House, The Queen's Drive, Exeter, Devon, EX4 4QL .....
.....
Country : United Kingdom .....
Phone : 01392 726131 Fax :xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Email : sjh217@exeter.ac.uk

2. CONTEXT OF PHQ USE

Individual clinical practice ☐

Research study √☐ Project ID/Protocol ID 09/H0202/64 _____

3. STUDY FINANCING

- Not funded academic research, medical practice[1] √☐[1]
- Funded academic research[2] ☐[2]
- Commercial study[3] ☐[3]

[1] *Not funded academic research: project not explicitly funded, but funding comes from overall departmental funds or from the University or individual funds.*

[2] *Funded academic research: projects receiving funding from commerce, government, EU or registered charity. Funded academic research– sponsored by industry fits the "commercial study[3]" category.*

Granting / Sponsoring from (if any) *(name of the governmental/foundation/company or other funding/sponsoring source):* .....
.....

[3] *Commercial studies (industry, CRO, any for-profit companies)*

PART 4. VERSIONS

Please indicate which version of the PHQ is needed:

PHQ Screener ☐ Brief PHQ Screener ☐ PHQ-9 Depression Screener√☐

Other version ☐ Please indicate which version:

PART 5. TRANSLATIONS

Please indicate in which language(s) and for which country(ies) the PHQ is needed:

Version:	*Language:*	*For use in the following country*	*Version:*	*Language:*	*For use in the following country*
PHQ-9	*English*	*USA*	PHQ-9	*English*	United Kingdom
e.g. PHQ	*Spanish*	*USA*			

Note: The PHQ translation(s) may not be available in the countries requested.

Please check availability and status of translations with MAPI Research Trust.

On behalf of Pfizer Inc., MAPI Research Trust grants "User" the right to use and reproduce the PHQ in the countries listed in section 5 subject to the following terms, conditions, and only upon signature of this agreement by both user and MAPI Research Trust:

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- the reference publications in reference section of the paper/presentation
- PHQ © 1999 Pfizer Inc. All rights reserved.

1.4. Copyright notice

"User" is required to place Pfizer Inc.'s copyright notice "PHQ © 1999 Pfizer Inc. All rights reserved" on all copies of the questionnaires distributed or used by "User".

2. Fees

2.1. Processing fees (MAPI Research Trust)

- The use of the **PHQ in commercial studies involving "for-profit" organizations** is subject to a distribution fee payable to MAPI Research Trust, of an amount of 500 (five hundred) Euro per study plus an additional 150 (one hundred and fifty) Euro per language version requested.
- The use of the **PHQ in funded academic research** is subject to a distribution fee payable to MAPI Research Trust, of an amount of 300 (three hundred) Euro per study plus an additional 50 (fifty) Euro per language version requested.
- The use of the **PHQ in non funded academic research and clinical practice** is free of charge.

"User" understands that those fees are paid to MAPI Research Trust and are not forwarded or paid to Pfizer Inc. who is granting usage rights in the tool to User free of charge.

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Upon execution of this Agreement, MAPI Research Trust shall promptly provide "User" with a definitive invoice, and "User" shall pay the invoice within thirty (30) days of the date indicated on the invoice.

3. Copyright

- "User" hereby acknowledges that Pfizer Inc. owns all copyright in the PHQ and in all derivative PHQ versions including but not limited to existing and future translations of the PHQ.
- "User" acknowledges Pfizer Inc.'s copyright in the PHQ and shall not contest such copyright or perform any act or omission adverse to such exclusive right.

- If, at any time during the term of this agreement, "User" learns of any infringement by a third party of any Intellectual Property Rights in connection with the PHQ "User" shall promptly notify MAPI Research Trust. MAPI Research Trust shall notify such infringement to Pfizer Inc. Pfizer Inc. shall have complete discretion whether to take further action and need not advise "User" of its decision.

4. Copy of Agreement

It is understood that a copy of this User Agreement may be provided to Pfizer Inc.

5. Questionnaire data

All data, related results and reports obtained by "User", or prepared by "User" in connection with use of the PHQ under this agreement shall remain the "User"'s property.

6. Liability

In the event of total or partial breach by MAPI Research Trust of any of its obligations hereunder, MAPI Research Trust's liability shall be limited to the direct loss or damage (excluding loss of profit and operating losses) suffered by "User" as a result of such breach and shall not include any other damages and particular consequential damages. Pfizer Inc. and its affiliates shall have no liability to "User" in said event.

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6.1. In the event of non-renewal of this Agreement

In the event of non-renewal of this Agreement by MAPI Research Trust for any cause or failure by MAPI Research Trust to conclude a new agreement with "User" upon the expiry of this Agreement, neither MAPI Research Trust, nor Pfizer Inc. or its affiliates will have no liability for payment of any damages and/or indemnity to "User".

7. Confidentiality

- MAPI Research Trust and "User" acknowledge that each party in connection with the terms of this agreement may obtain certain information, which is confidential and/or property to the other party in the course of its use of PHQ.
- All and any information related to the PHQ including but not limited to the following: information concerning clinical investigations, creations, systems, materials, software, data and know-how, translations, improvements ideas, specifications, documents, records, notebooks, drawings, and any repositories or representation of such information, whether oral or in writing or software stored, are herein referred to as confidential information.
- In consideration of the disclosure of any such confidential information to the other, each party agrees to hold such confidential information in confidence and not divulge it, in whole or in part, to any third party except for the purpose specified in this agreement.

8. Use of name

It is agreed that MAPI Research Trust shall not disclose, whether by the public press or otherwise, "User"'s Company name or "User"'s name (if "User" is not a company), to any third party except to Pfizer Inc, copyright owner of the PHQ.

9. Term and termination

- This agreement shall be effective as of the date of its signature by "User" and shall continue until the conclusion of the study mentioned above in section 2.
- Either party may terminate this Agreement immediately upon providing written notice to the other party in the event of: (a) the other party's unexcused failure to fulfill any of its material obligations under this Agreement or (b) upon the insolvency or bankruptcy of, or the filing of a petition in bankruptcy or similar arrangement by the other party.

10. Assignment

This Agreement and any of the rights and obligations of "User" are specific to the "User" and cannot be assigned or transferred by "User" to any third party or by operation of law, except with the written consent of Pfizer Inc.

11. Separate Agreement

This Agreement holds for the above mentioned context only. User acknowledges that use of the PHQ in any additional project of the "User" will require a separate agreement.

12. Entire Agreement, Modification, Enforceability

- The entire agreement hereto is contained herein and this Agreement cancels and supersedes all prior agreements, oral or written, between the parties hereto with the respect to the subject matter hereto.
- This Agreement signed by both parties or any of its terms may not be changed or amended except in a written document signed by both parties and the failure by either party hereto to enforce any or all of the provision(s) of this Agreement shall not be deemed a waiver or an amendment of the same and shall not prevent future enforcement thereof.
- If any one or more of the provisions or clauses of this Agreement are adjudged by a court to be invalid or unenforceable, this shall in no way prejudice or affect the binding nature of this Agreement as a whole, or the validity or enforceability of each/and every other provision of this Agreement.

13. Governing law

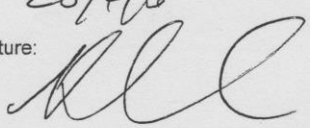
This Agreement is made in and shall be governed by and interpreted in accordance with the substantive laws of France, without regard to conflicts of laws.

14. Forum

Any controversy arising under this Agreement if litigated, shall be adjudicated in the court of the competent jurisdiction in Lyon, France, notwithstanding the plurality of defendants or claim in warranty, even in the event of emergency procedures or protective procedures, and the parties hereby submit to the exclusive jurisdiction of such court.

IN WITNESS WHEREOF, the party hereto has caused this Agreement to be executed by its duly authorised representative as of the date first above written.

AGREED BETWEEN:

Company: University of Exeter Name: Prof. Ken Evans Date: 26/4/10 Signature: 	MAPI Research Trust Name: Date: Signature:

Appendix 14

Anxiety Questionnaire GAD-7

Participant ID ..... Participant initials.....

Date.....

Is this your:
1st Appointment
6 week Appointment
6 month Appointment
12 month Appointment

Over the last 2 weeks, how often have you been bothered by the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
Feeling nervous, anxious or on edge	☐ 0	☐ 1	☐ 2	☐ 3
Not being able to stop or control worrying	☐ 0	☐ 1	☐ 2	☐ 3
Worrying too much about different things	☐ 0	☐ 1	☐ 2	☐ 3
Trouble relaxing	☐ 0	☐ 1	☐ 2	☐ 3
Being so restless that it is hard to sit still	☐ 0	☐ 1	☐ 2	☐ 3
Becoming easily annoyed or irritable	☐ 0	☐ 1	☐ 2	☐ 3
Feeling afraid as if something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3

Total Score _____ = **Add Columns** ____ + ____ + ____

If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

The GAD-7 was developed by Drs. Robert L. Spitzer, Kurt Kroenke, Janet B.W. Williams, and Bernd Löwe. For research information, contact Dr. Spitzer at rls8@columbia.edu.

RE: GAD-7 Questionnaire

Request For Permissions [RequestForPermissions@pfizer.com]

Sent: 03 December 2009 12:42

To: Hopkins, Susan

Cc: Ungaro, Jane [Jane.Ungaro@Pfizer.com]

Dear Sue,

Pfizer is pleased to give permission for the requested uses. Please use the following notice:

GAD-7 Copyright Pfizer Inc. all rights reserved; used with permission.

Best regards,

Rosalba Oliveri
Trademark Specialist
Pfizer Inc. --Trademark Department
Mail Stop: 150/2/112
150 East 42nd Street, New York, NY 10017
direct 212.733.1120 | fax 212.573.2273
rosalba.oliveri@pfizer.com

From: Hopkins, Susan [mailto:sjh217@exeter.ac.uk]
Sent: Thursday, December 03, 2009 5:08 AM
To: Request For Permissions
Subject: GAD-7 Questionnaire

Dear Sirs,

Re: GAD-7 Questionnaire

I am a PhD student undertaking a research project at the University of Exeter. I would like to use the GAD-7 questionnaire as part of the study and would be grateful for your permission to do so.

Yours faithfully

Sue Hopkins
PhD Researcher
School of Engineering, Mathematics and Physical Sciences
University of Exeter
E mail: sjh217@exeter.ac.uk

Appendix 15

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

Participant ID ..... Participant initials.....

Date.....

Is this your:

1st Appointment ☐

6 week Appointment ☐

6 month Appointment ☐

12 month Appointment ☐

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

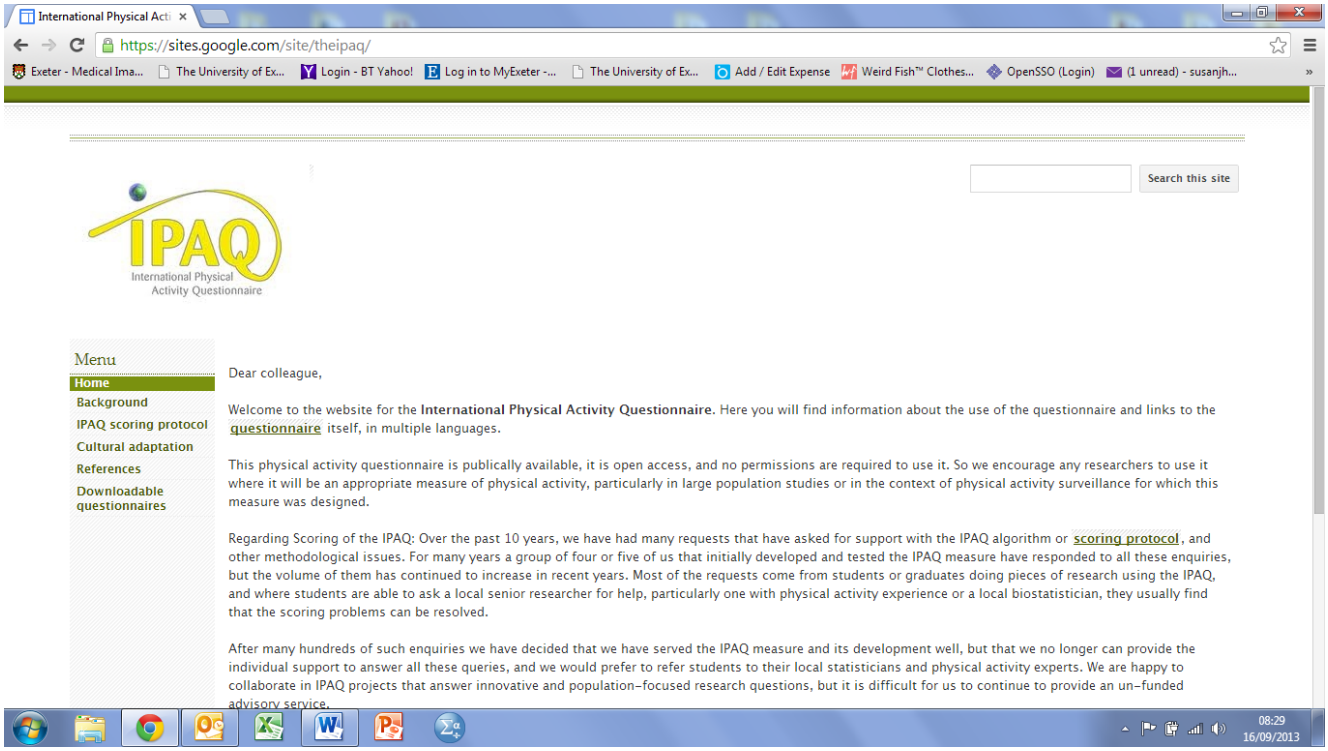
_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Appendix 15


International Physical Acti
https://sites.google.com/site/theipaq/
Exeter - Medical Ima...
The University of Ex...
Login - BT Yahoo!
Log in to MyExeter -...
The University of Ex...
Add / Edit Expense
Weird Fish™ Clothes...
OpenSSO (Login)
(1 unread) - susanjh...
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Downloadable questionnaires
Dear colleague,
Welcome to the website for the International Physical Activity Questionnaire. Here you will find information about the use of the questionnaire and links to the questionnaire itself, in multiple languages.
This physical activity questionnaire is publically available, it is open access, and no permissions are required to use it. So we encourage any researchers to use it where it will be an appropriate measure of physical activity, particularly in large population studies or in the context of physical activity surveillance for which this measure was designed.
Regarding Scoring of the IPAQ: Over the past 10 years, we have had many requests that have asked for support with the IPAQ algorithm or scoring protocol, and other methodological issues. For many years a group of four or five of us that initially developed and tested the IPAQ measure have responded to all these enquiries, but the volume of them has continued to increase in recent years. Most of the requests come from students or graduates doing pieces of research using the IPAQ, and where students are able to ask a local senior researcher for help, particularly one with physical activity experience or a local biostatistician, they usually find that the scoring problems can be resolved.
After many hundreds of such enquiries we have decided that we have served the IPAQ measure and its development well, but that we no longer can provide the individual support to answer all these queries, and we would prefer to refer students to their local statisticians and physical activity experts. We are happy to collaborate in IPAQ projects that answer innovative and population-focused research questions, but it is difficult for us to continue to provide an un-funded advisory service.
08:29
16/09/2013

Appendix 16

Risk and Benefit Assessment

OBJECTIVE: The current research available on disuse osteopenia, particularly long-term unilateral disuse osteopenia is limited. Correct diagnosis means patients can be monitored and treated, reducing their future fracture risk. Most research is focused on spinal cord injury, stroke patients, astronauts and bed-rest volunteers and may not be directly comparable to the effects of immobilisation of a single limb. This research aims to investigate long-term disuse osteopenia in a wider population, including the fracture prevalence, and possible therapeutic interventions to provide a reduction in long-term low energy trauma fracture risk. This is an important consideration for all healthcare teams caring for patients with long-term limb immobilization.

OUTCOMES: Knowledge regarding the effects of immobilization on bone density and the resulting effect on future fracture risk. The effects of immobilization on functionality, quality of life and mental health (with regard to depression and anxiety) will also be investigated.

EVIDENCE: Disuse osteopenia or osteoporosis is a well recognised complication of immobilisation[1-4]. In the majority of patients there is reversal of the disuse osteopenia upon remobilisation[5]. However, stress fractures distal to the acute fractures have been reported in a small minority of patients post lower limb fracture upon mobilisation[6]. Low energy trauma fractures have been reported in the lower-limb long-bones of paraplegics[7,8] and in non-ambulatory children with congenital conditions[9], demonstrating that disuse osteopenia results in an increased fracture rate.

There are few studies investigating disuse osteopenia in single limbs. Tandon *et al.*[10] reported reduced disuse osteopenia following external fixation of the tibia compared to those placed in plaster of Paris, even though those who underwent external fixation had more severe fractures. Marchetti *et al.*[11] reported disuse osteopenia following shoulder surgery, which was partially reversed six weeks following remobilisation, whilst Rüegsegger *et al* [12] reported bone loss bilaterally post total hip replacement. One of the most frequently studied groups suffering disuse osteoporosis are astronauts following time spent in microgravity during space missions. Lang[13] reported that up to 15% of bone strength can be lost at the proximal femur over a 6 month flight. Rapid and severe bone loss has also been reported in patients suffering stroke[14] and in volunteers on bed-rest studies[15].

Studies of bed-rest volunteers and spinal cord injury (SCI) patients have consistently reported an increase in markers of global bone resorption[15]. However, in most studies the markers of bone formation have remained unchanged, suggesting that there is no decrease in bone formation as a result of disuse osteopenia[15,16]. Maimoun *et al.* studied the effects of disuse osteopenia on osteoprotegerin (OPG) and reported that OPG was stimulated in SCI patients, whilst Receptor Activator for Nuclear Factor kB Ligand (RANKL) was inhibited. These results led them to hypothesise that OPG may provide a protective mechanism in the body. Whilst the OPG was deemed to have a protective role in this study, patients still lost bone and bone resorption markers were elevated, suggesting that the stimulation of OPG is insufficient to prevent osteoclastic proliferation and bone resorption[16]. Studies of bed-rest volunteers have also reported increased urinary and faecal excretion of calcium coupled with increased serum calcium and decreased intestinal calcium absorption. Increased serum calcium results in low parathyroid hormone and vitamin D, a regulatory response to the increased bone resorption, which results in a decreased intestinal calcium absorption through the vitamin D-mediated pathway[15,17-19].

Nutritional interventions have been reported to have a small influence of addressing the negative calcium balance in disuse osteopenia[20]. Early remobilisation is the most important factor for the prevention of disuse osteopenia[7]. However, in patients where this is not possible, other therapeutic interventions may be required. The bisphosphonate tiludronate has been demonstrated to be an effective treatment for disuse osteoporosis in paraplegic patients[21], whilst alendronate has been demonstrated to be well tolerated and effective in non-ambulatory children[9]. In an animal study Ma *et al*[22] reported increases in trabecular bone in the tibiae of rats with continuously immobilised hind legs treated with 1,38 human parathyroid hormone (hPTH), suggesting this could be an effective treatment for disuse osteopenia. It is possible that non-pharmacological therapeutic interventions might improve

disuse osteopenia such as weight-bearing exercise, or vibrating plates, both of which have been demonstrated to have positive effects on bone density[23,24].

In conclusion, the current research available on disuse osteopenia, particularly long-term unilateral disuse osteopenia is limited. Correct diagnosis means that patients with this condition can be monitored and treated, reducing their future fracture risk. Most research is focused on SCI, stroke patients, astronauts and bed-rest volunteers and may not be directly comparable to the effects of immobilisation of a single limb. Further research is required to investigate long-term disuse osteopenia in a wide population, including the fracture prevalence, and possible therapeutic interventions to provide a reduction in their long-term low energy trauma fracture risk. This is an important consideration for all healthcare teams caring for patients with long-term limb immobilisation and long-term future fracture risk and appropriate therapeutic intervention requires consideration.

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BENEFITS/HARMS: All scans will be conducted on a GE Lunar Prodigy machine, to ensure fast scan time with a low as possible radiation dose. The radiation doses each participant will be subjected to during a Lunar scan are detailed in Table 1, with comparative risks identified in Table 2.

Table 1. Radiation doses from DEXA compared to other activities

	Effective dose (μSv)
AP spine*	0.7
Hip*	0.68
Total body*	0.5
Lateral spine*	0.6
Chest x-ray	20
Lateral lumbar spine x-ray	700
Daily background radiation	6 – 20 (depending on location)
Return transatlantic flight	80

*GE Lunar scan doses for a typical patient size using standard mode

Table 2. Activities carrying a risk comparable to receiving an effective dose of 10 μSV from a DEXA scan*

Exposure to natural background radiation for 2 days
Smoking a cigarette
Travelling 30miles by car
Travelling 150miles by aeroplane
Working in a factory for a week

*The Lunar Prodigy protocol of scanning bilateral hips, AP spine and whole body equates to = 2.56 μSv. Indeed, the annual risk of death by natural causes (age 40) is 1 in 700, whilst the risk of death from an effective dose of 2μSv is 1 in 10 million.

The University of Exeter Dose constraints (DXA laboratory IRMER procedures) are reproduced below as Table 4. (The dose constraints are derived from ICRP62 and the Medical and Dental Guidance Notes, and are identical to those employed within the Royal Devon and Exeter Foundation NHS Trust). As may be seen the level of risk for a 2 μSv effective dose is classified as trivial.

Participants in the study will be post-menopausal females above 45 years old. Four repeat sets of scans are required at baseline, 6 week, 6 month and 12 month intervals giving a total effective dose of 10.4 μSv. Only three sets of scans are required for control participants giving a total effective dose of 7.8 μSv.

The dose constraint for this trial has been set as 15 μSv, allowing for the possible repeat of individual exam(s) in the (unlikely) event of technical failure.

In accordance with IRMER (2000), CHERC has a network of qualified experts in place to ensure any one person participating within a research project is not exposed to unnecessary risk. The network is detailed below;

Position	**Name(s)**	**Employer**
Employer	Professor Steve Smith	University of Exeter
Referrer	Dr Gill Vivian	Derriford Hospital
Practitioner	Dr Gill Vivian	Derriford Hospital
Operators	Dr Karen Knapp, Dr Joanne Welsman, Mr David Childs, Dr Ann Rowlands	University of Exeter
Medical Physics Expert	Dr Bob Ward	Royal Devon and Exeter Hospital
Radiation Protection Adviser	Ms Sonia Nuttall	External Advisor
Radiation Protection Supervisor	Mr David Childs	University of Exeter

The practitioner and operator are as defined in CHERC's IRMER (2000) compliance document. As part of the Research Ethics Committee approval process for research projects, the Practitioner provides generic justification for exposures identified in that research proposal. All participants will then be assessed by the operators using osteoporotic risk factor and contra-indication questionnaires to assess the suitability for a scan. In cases where the person undergoing the procedure benefits from the exposure, the Practitioner is required to plan individual target levels of dose. These are set at the time of justification and take into account the age of the individual and any other factors which affect the risk of that examination. In cases where there is no benefit to the individual, the setting of a dose constraint is required. This is determined from the level of benefit to society and is detailed in Table 4.

PROCEDURE FOR REFERRAL: If a participant is diagnosed with a BMD value (T or Z score[†]) that classifies them as Osteopenic or below according to the appropriate criteria (i.e., WHO criteria (see Table 3), NHANES criteria) they will be referred, by the operator, to the practitioner for further advice and possible intervention.

Table 3. World Health Organisation Criteria for Interpretation of DEXA scans

Diagnostic categories*	**Definitions**
Normal	A value for BMD within 1SD of the young adult reference mean.
Osteopenic	A value for BMD more than 1SD below the young adult mean but less than 2.5SD below this value. A T score between –1.0 and –2.5.
Osteoporosis	A value for BMD more than 2.5SD below the young adult mean. A T score below –2.5.
Severe Osteoporosis	A value for BMD more than 2.5SD below the young adult mean in the presence of one or more fragility fractures.

*According to the T score

CONCLUSIONS:

The current research available on disuse osteopenia, particularly long-term unilateral disuse osteopenia is limited. Correct diagnosis means patients can be monitored and treated, reducing their future fracture risk. Most research is focused on spinal cord injury, stroke patients, astronauts and bed-rest volunteers and may not be directly comparable to the effects of immobilisation of a single limb. This research aims to investigate long-term disuse osteopenia in a wider population, including the fracture prevalence, and possible therapeutic interventions to provide a reduction in long-term low energy trauma fracture risk. This is an important consideration for all healthcare teams caring for patients with long-term limb immobilization. The research and risk and benefit assessment suggests that the GE Lunar Prodigy could give the greatest benefit with least side effects in participants when assessing osteoporosis risk.

[†] T score: This represents the number of SD between the participants BMD and the mean reference value for the young sex-matched adults with peak BMD; Z score: This represents the number of SD between the BMD and the mean value of a sex and age matched population.

Table 4. Determination of benefit versus risk

Required benefit to Society	Dose Constraint 1 † (μSv)	Dose Constraint 2† (μSv)	Dose Constraint 3† (μSv)	Level of risk
Minor	30	100	500	Trivial
Intermediate	160	500	2500	Minor
Moderate	1600	5000	25,000	Intermediate
Substantial	3300	10,000	50,000	Moderate

†These constraints apply to; 1 – children; 2 - adults under 50 years; 3 – adult over 50 years.

Definitions of Benefit

Minor: expected only to increase knowledge.
Intermediate: related to increases in knowledge leading to health benefit.
Moderate: aimed directly at the diagnosis, cure or prevention of disease.
Substantial: directly related to the saving of a life or prevention/mitigation of serious disease.

Appendix 17

ACTIVITY MONITOR INSTRUCTIONS

Participant ID ..... Participant initials.....
Date.....

Is this your:	
1st Appointment	
6 week Appointment	
6 month Appointment	
12 month Appointment	

The activity monitor (pedometer) is a small, plastic box that records how much you are moving. We will use this information to assess how active you are when you are wearing it.

PLEASE

- **WEAR IT FOR 3 DAYS and return it with this form in the envelope provided.**
- Wear the monitor all day (from getting up until bed time).
- Wear it on your dominant side (i.e. right if you are right handed, left if left handed) OR on your uninjured side if you have had a fracture or surgery.
- Do not wear whilst showering, bathing or swimming.
- Press the RESET button at the start of each day (display will show 0).
- Please record the reading (in the boxes below) at the end of each day.

DAY 1	
DAY 2	
DAY 3	

Appendix 18

Immobilization record

Participant ID ..... Participant initials.....

Date.....

Is this your:
1st Appointment
6 week Appointment
6 month Appointment
12 month Appointment

Since your last appointment for this study:-

Have you been fully mobile throughout the entire period?

No
Yes

If yes, please indicate approximately how much weight bearing activity you have done, on average, per day
.....

Have you been partially immobilized for any period?

No
Several days Please state how many.....
1 week
2 weeks
More than 2 weeks Please state how many.....

Please indicate approximately how much weight bearing activity you have done, on average, per day
whilst partially immobilized
.....

Have you been totally immobilized for any period?

No
Several days Please state how many.....
1 week
2 weeks
More than 2 weeks Please state how many.....

Appendix 19

Treatment and falls record

Participant ID ..... Participant initials.....

Date.....

Is this your:
1st Appointment
6 week Appointment
6 month Appointment
12 month Appointment

Since your last appointment for this study:-

Have you had any falls during this period?
No
Yes
If yes, please give details
.....
..
Have you sustained another fracture during this period?
No
Yes
If yes, please give details
.....
..

Have you been put onto any drug treatment for osteoporosis during this period?
No
Yes
If yes,
When did your treatment start?.....
What drug(s) have you been prescribed?.....
What is the dosage per day?.....

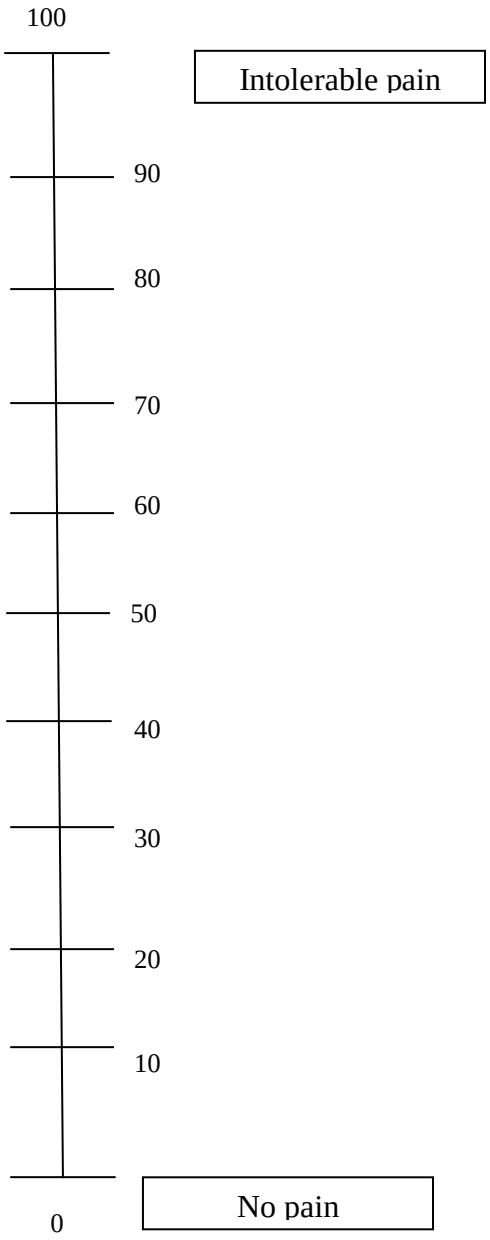
Have you been put onto any other medication during this period?
No
Yes
If yes,
When did your treatment start?.....
What drug(s) have you been prescribed?.....
What is the dosage per day?.....

Have you undergone any physical therapy for osteoporosis during this period?
No
Yes
If yes,
When did your treatment start?.....
What therapy have you been having?.....
How often do you receive this therapy?.....

Have you undergone any other form of physical therapy during this period?
No
Yes
If yes,
When did your treatment start?.....
What therapy have you been having?.....
How often do you receive this therapy?.....

Have you been taking pain killers during this period?
No
Yes
If yes,
What medication have you used?.....
Dose taken per day (on average)?.....
How many weeks have you been using this medication?.....

Please indicate by drawing a line on the scale below, what level of pain you experience on an average day. 100 represents intolerable pain. 0 represents no pain at all.



Appendix 20

MOOD DISORDERS CENTRE
PROTOCOL FOR ASSESSING AND REPORTING RISK

The following principles and procedures govern risk assessment and reporting in the Mood Disorders Centre (MDC). The MDC does not manage risk.

General principles

MDC clinical academic faculty are responsible for risk assessment in their research programmes. This includes ensuring that staff, students and interns working with them receive adequate induction and training prior to participant contact in which risk could be disclosed and ongoing supervision during their research work.

Many of the research projects in the MDC will include supplementary and more detailed protocols for risk assessment.

The AccEPT Clinic Lead (for new assessments) and clinic therapists (for patients in therapy) are responsible for risk assessment in the AccEPT clinic.

General procedures

Background training materials are available on the shared directory.

Whenever any significant risk is identified a risk assessment should be completed and (counter-) signed by the responsible member of staff. If at all possible this should be done at the time of the assessment, or as soon afterwards as possible.

Any significant, but not imminent risk should be reported to the person's GP and, if appropriate, other health care professionals, as soon as is reasonably possible.

For research outside of the local area, PIs / supervisors should familiarise themselves with the local providers' risk procedures, and researchers should hold the relevant contact details needed in the case of immediate risk.

When clinical academic staff are away from the Centre they should ensure appropriate cover is arranged for any risk issues that might arise in their absence.

Appendix 20

When conducting telephone interviews in which risk may be disclosed, the interviewer should establish the location of the participant at the start of the call, and clarify the boundaries of confidentiality (as per trial / clinic protocol).

Applying MDC Risk Protocol to the AccEPT Clinical Service

Typically risk may be detected at three stages during a client's contact with the clinic:

1. At telephone screening

2. At face-to-face assessment

3. During therapy, and before discharge from the Clinic.

1. Telephone screening

The MDC risk protocol should be enacted if any of the following boxes in section 2.1 are ticked:

Hopeless/Suicide

☐ Feeling hopeless or suicidal ☐ Feeling persists

☐ Considered self-harm ☐ Did self-harm

The outcome should be recorded in the telephone interview form.

Staff / interns undertaking telephone screening under supervision should ensure they seek supervision for any risk assessments and have their reports and letters countersigned.

2. At face-to-face assessment

Client should be asked directly about whether suicidal ideation is present (usually as part of the current SCID, unless he / she is not currently experiencing depression). If there is any indication that this is the case from questioning / discussion, or from scores on self-report measures (score > 0 on CORE item 6 or PHQ-9 item 9 or BDI-II item 9), the risk protocol should be enacted.

Particular attention should be paid to checking whether any client who reported significant levels of risk at the telephone assessment (action taken was B) have spoken with his / her GP (see protocol).

The outcome of any risk assessment (including action taken) should be recorded in the client's notes and communicated to the GP or others involved in the patient's care as appropriate Staff / interns undertaking assessments under supervision should ensure they seek supervision for any risk assessments and have their reports and letters countersigned.

3. During therapy

In individual therapy sessions risk should be assessed for clients reporting current suicidal ideation (either through questionnaire responses or during therapy discussion), following the MDC protocol.
Group interventions should specify the trigger for further investigation of risk (for example, in the BA group risk is assessed if the client scores above 1 on BDI-II item 9, or changes from 0 to 1 on this item) and should assess risk using the MDC protocol.

Clinicians are expected to exercise clinical judgment in determining suitable strategies for reporting and managing risk with regard to individual clients whose level of risk is assessed as being at 'B'. For clients at immediate risk, the MDC risk protocol should be followed.

Therapists are responsible for discharging patients back to the care of their GPs as soon after therapy is concluded as possible. This discharge summary should include reporting any risk issues, so that GPs can manage patient's safety as part of their care plan.

Exeter emergency contact numbers

- Crisis Resolution Home Treatment Team (East and Mid Devon) 07968 845048

Please note, this number is to make an urgent referral to the Crisis Team and should not be given out to participants / clients / members of the public under any circumstances. The participant's / client's GP can also make an urgent referral to the Crisis Team and should be the first port of call.

- Exeter Accident and Emergency Department

This is located at the Royal Devon and Exeter Hospital (Wonford), Barrack Road, Exeter, EX2 5DW

Exploring Risk in Research Interviews

THOUGHTS

"I see that you've said / you mentioned that……. These are thoughts / feelings that people suffering from depression often have, but it's important to make sure you are receiving the right kind of support. So if it's OK, I would now like to ask you some more questions that will explore these feelings in a little more depth."

PLANS

1 Do you know how you would kill yourself? Yes / No

If **yes –** details

---

2 Have you made any actual plans to end your life? Yes / No

If **yes –** details

ACTIONS

3 Have you made any actual preparations to kill yourself? Yes / No

If **yes –** details

---

4 Have you ever attempted suicide in the past? Yes / No

If **yes –** details

PREVENTION

5 Is there anything stopping you killing or harming yourself at the moment? Yes / No

If **yes –** details

---

6 Do you feel that there is any immediate danger that you will harm or kill yourself? Yes / No

Details:

FOLLOW-UP FROM PREVIOUS CONTACT

7 **If Action B was enacted at previous assessment and level B risk is identified at current assessment**: Last time we met I suggested that you spoke to your GP about these thoughts, and I also wrote to your GP about this. Have you been able to speak with your GP about these thoughts since we last met? Yes / No

See risk table overleaf for appropriate actions

Appendix 20

Researcher Risk Protocol

To be used following any indication of risk from questionnaire items, responses to interview questions or any other sources. Look at answers from the sheet to determine the level of risk, A B or C:

Actions by Researcher	***Tell Participant***
All answers 'no' apart from Q5 'yes': ↓ **A** →	*I can see that things have been very difficult for you, but it seems to me these thoughts about death are not ones you would act on – would this be how you see things? (if they say yes) I would advise you to make an appointment to see your GP to talk about these feelings* ***(as per trial protocol)***.
'Yes' for any **one** of Qs 1-4; plus 'yes' for Q5 and 'no' for Q6 ↓ **B1** →	*Things seem to be very hard for you right now and I think it would help if you were to speak to your GP about these feelings. I will be writing to your GP to tell them that you have been here today and have been having some troubling thoughts. I would also advise you to make an appointment to see your GP to talk about these feelings. (**as per trial protocol**).*
'Yes' for any **one** of Qs 1-4; plus 'yes' for Q5 and 'no' for Q6 **and** 'no' to Q7 ↓ B2 →	*I think it's important that your GP knows how difficult things are for you right now. I will be telephoning your GP to speak with him/her and suggest that you meet with one another. I also advise that you make an appointment to see your GP to talk about these feelings. **(as per trial protocol**).N.B: telephone call to GP to be followed up by letter. The letter should include the statement "*the clinical management of this patient remains your responsibility, but it is part of our protocol to inform you of any risks disclosed to ourselves so that you can take account of them in your care plan.*"*
Scoring 'no' to Q5 or 'yes' to Q6 ↓ **C** Actively Suicidal →	*I am very concerned about your safety at this moment, I am not a clinician but I would like you to talk to one right now. I am going to make some telephone calls now to arrange for your GP Care Co-ordinator / Crisis Management team/the emergency services to let them know how you are feeling and to arrange for you to receive immediate help.*

Action to take in the case of immediate risk:
Participant needs immediate help – **do not leave them alone, or if on telephone, do not hang up**. Follow your trial's chain of supervisory clinical contact in order to involve supervisory clinician right away. Then (with clinician if possible) follow the chain of contact below:

1. GP / out of hours GP; if not
2.Crisis team; if not
3. Clinician accompanies to A&E; if not (or interview is over telephone)
4. Call ambulance.

Appendix 1 **Risk Report**

Patient name: _____ DOB: _____

Suicide risk information:

Include whether the participant has reported any of the following:

- *History of previous suicide attempts*
- *Current suicidal ideation*
- *Relevant inventory scores (e.g., BDI item 9)*
- *Suicide plans / preparations*
- *Protective factors*
- *Regular contact with GP?*

Date reported: ___/___/___

Additional notes / actions taken:

*As part of the MDC risk protocol, suicide risk is **managed** by the patient's GP.*

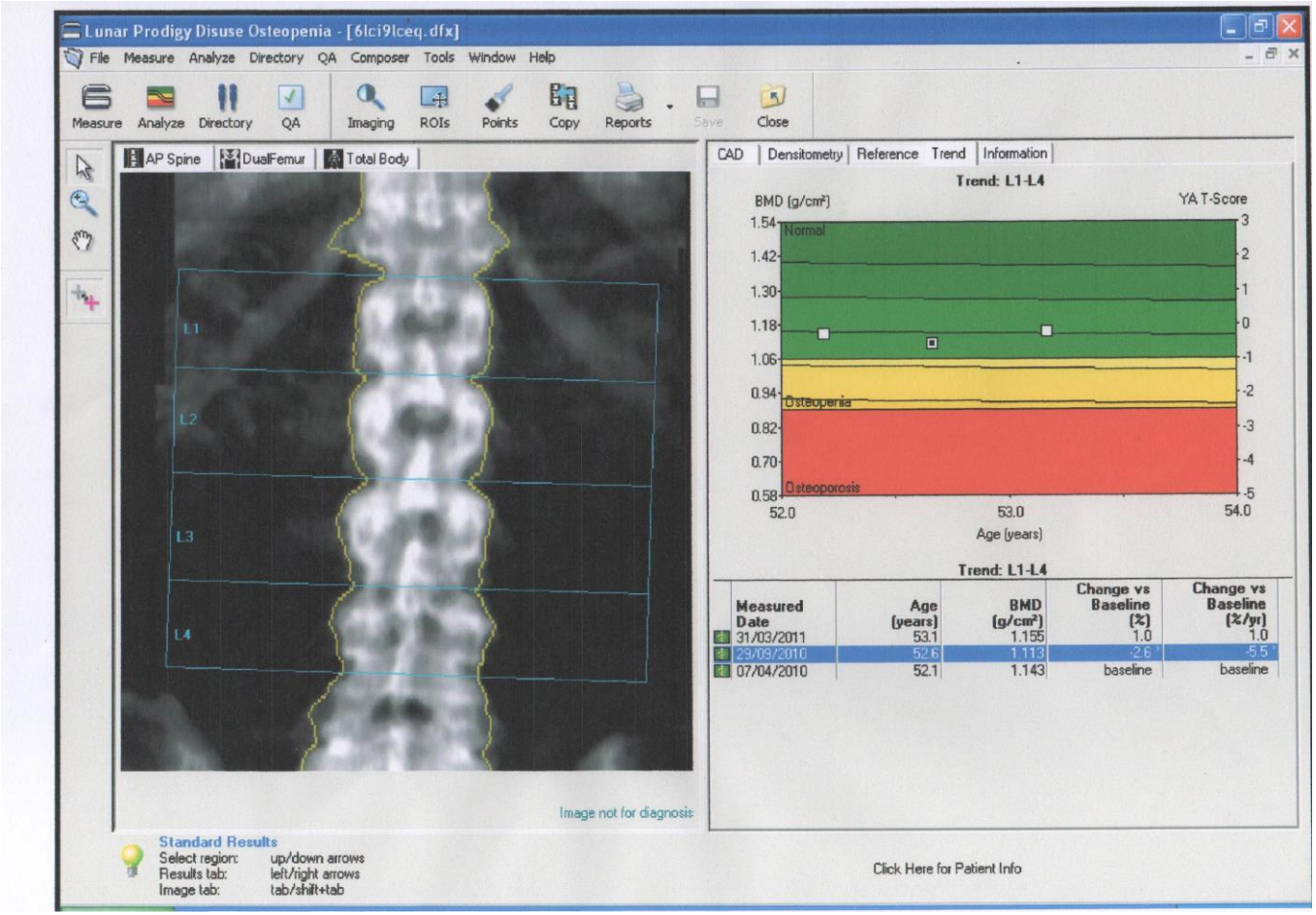
Date action taken: ___/___/___

Researcher / assessor: _____ Signed: _____ Date: ___/___/___

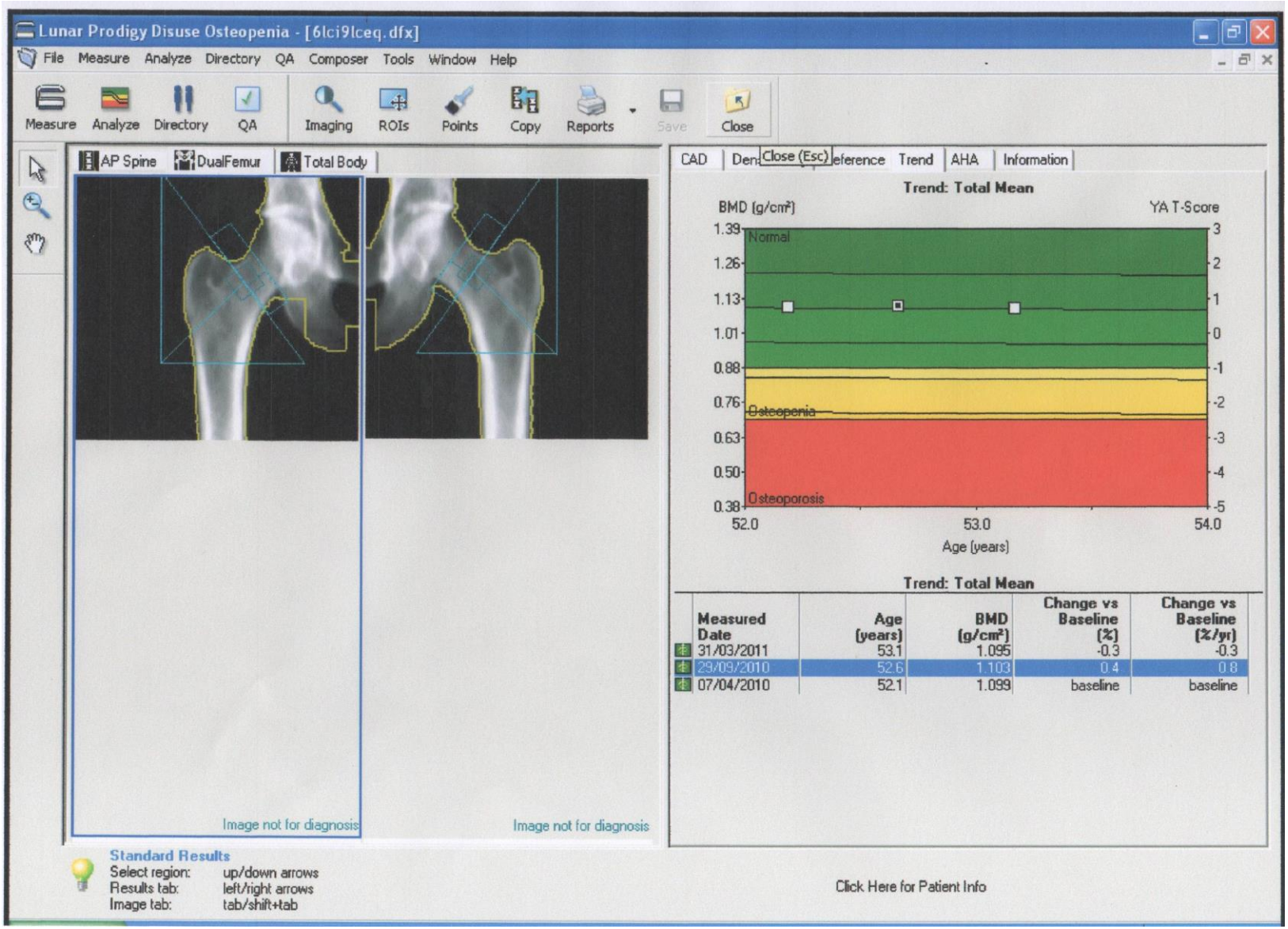
Supervisor: _____ Signed: _____ Date: ___/___/___

Appendix 21

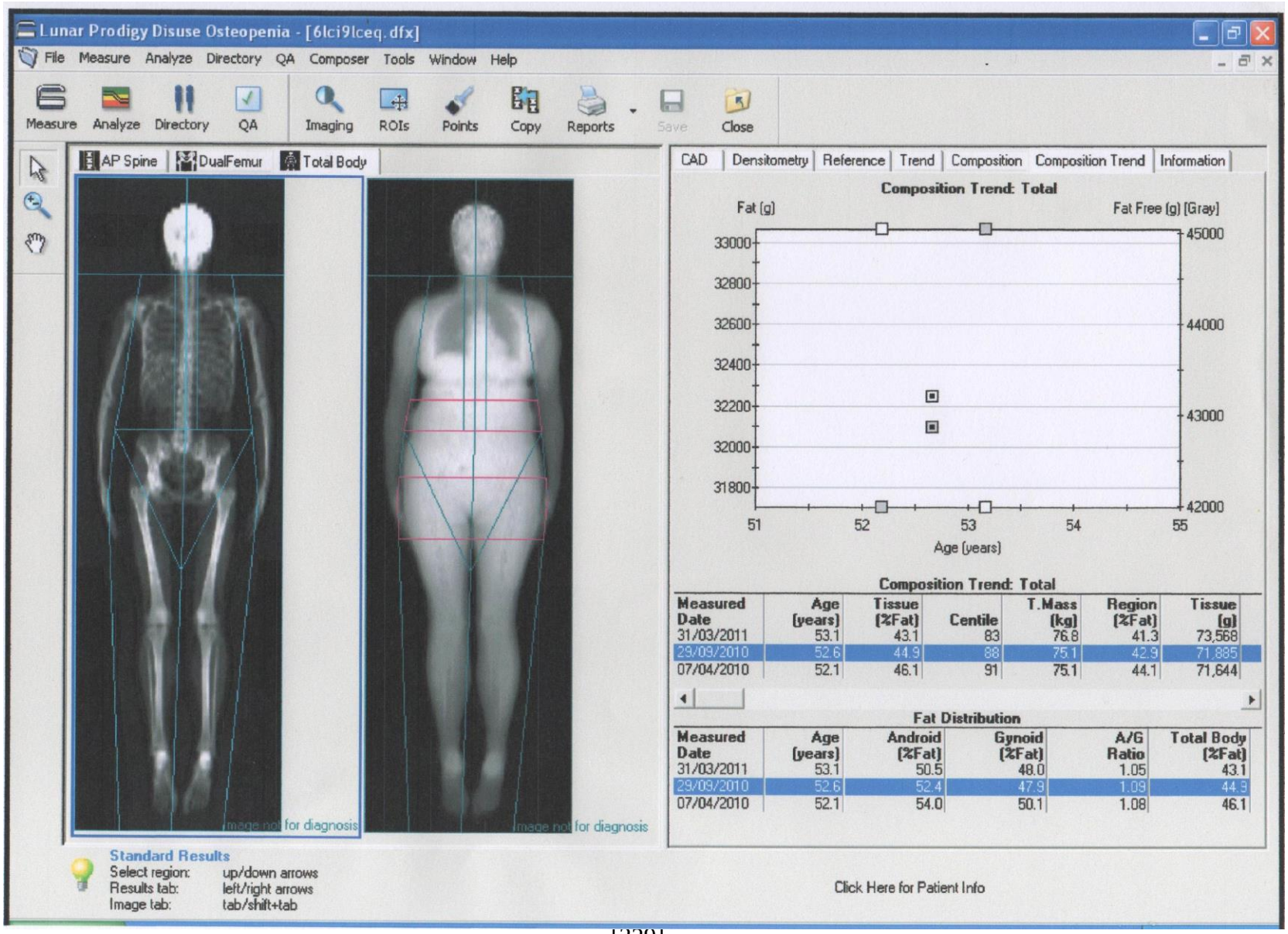
Example of the DXA output



Appendix 21


Lunar Prodigy Disuse Osteopenia - [6lci9lceq.dfx]
File Measure Analyze Directory QA Composer Tools Window Help
Measure Analyze Directory QA Imaging ROIs Points Copy Reports Save Close
AP Spine DualFemur Total Body
Image not for diagnosis
Image not for diagnosis
CAD Den Close (Esc) eference Trend AHA Information
Trend: Total Mean
BMD (g/cm²)
YA T-Score
Normal
Osteopenia
Osteoporosis
1.39 1.26 1.13 1.01 0.88 0.76 0.63 0.50 0.38
3 2 1 0 -1 -2 -3 -4 -5
52.0 53.0 54.0
Age (years)
Trend: Total Mean
Measured Date | Age (years) | BMD (g/cm²) | Change vs Baseline (%) | Change vs Baseline (%/yr)
31/03/2011 | 53.1 | 1.095 | -0.3 | -0.3
29/09/2010 | 52.6 | 1.103 | 0.4 | 0.8
07/04/2010 | 52.1 | 1.099 | baseline | baseline
Standard Results
Select region: up/down arrows
Results tab: left/right arrows
Image tab: tab/shift+tab
Click Here for Patient Info

Appendix 21


Lunar Prodigy Disuse Osteopenia - [6lci9lceq.dfx]
File Measure Analyze Directory QA Composer Tools Window Help
Measure Analyze Directory QA Imaging ROIs Points Copy Reports Save Close
AP Spine DualFemur Total Body
CAD Densitometry Reference Trend Composition Composition Trend Information
Composition Trend: Total
Fat (g)
Fat Free (g) [Gray]
33000
32800
32600
32400
32200
32000
31800
45000
44000
43000
42000
51
52
53
54
55
Age (years)
Composition Trend: Total
Measured Date | Age (years) | Tissue (%Fat) | Centile | T.Mass (kg) | Region (%Fat) | Tissue (g)
31/03/2011 | 53.1 | 43.1 | 83 | 76.8 | 41.3 | 73,568
29/09/2010 | 52.6 | 44.9 | 88 | 75.1 | 42.9 | 71,885
07/04/2010 | 52.1 | 46.1 | 91 | 75.1 | 44.1 | 71,644
Fat Distribution
Measured Date | Age (years) | Android (%Fat) | Gynoid (%Fat) | A/G Ratio | Total Body (%Fat)
31/03/2011 | 53.1 | 50.5 | 48.0 | 1.05 | 43.1
29/09/2010 | 52.6 | 52.4 | 47.9 | 1.09 | 44.9
07/04/2010 | 52.1 | 54.0 | 50.1 | 1.08 | 46.1
Image not for diagnosis
Image not for diagnosis
Standard Results
Select region: up/down arrows
Results tab: left/right arrows
Image tab: tab/shift+tab
Click Here for Patient Info

Appendix 22

Trabecular Bone Score (TBS) report example

Childrens Health and Exercise Research Centre

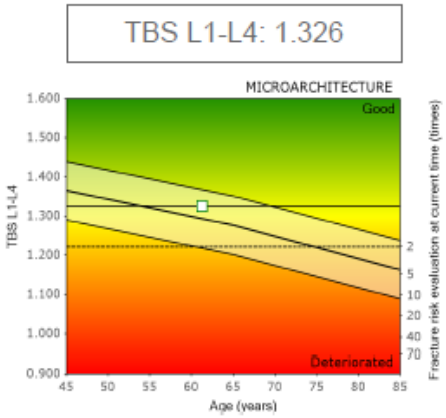
University of Exeter

Devon - EX1 - 2LU

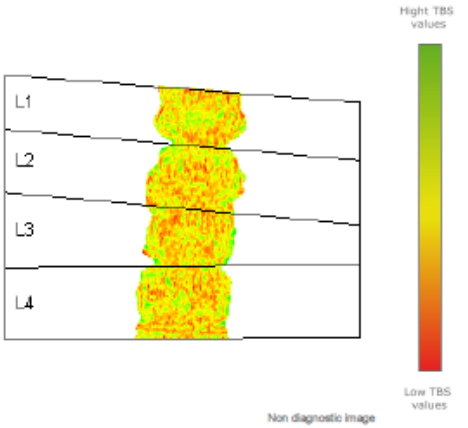
Patient:	[redacted]	Date of birth:	[redacted] 61.2 years
Height / Weight:	155.2 cm / 102.3 kg	DXA acquisition date:	[redacted] 13:50
Gender / Ethnicity:	Female / White	Prescribing doctor:	[redacted]

RACHIS TBS REPORT

TBS reference graphic(*)



TBS Cartography



Additional results

Region	TBS
L1	1.345
L2	1.320
L3	1.306
L4	1.333
L1-L4	1.326
L1-L3	1.324
L1-L2	1.333
L2-L4	1.320
L2-L3	1.313
L3-L4	1.320

Comments

(*): TBS reference graphic for the French Caucasian women

The TBS values (per bone region) and the cartography (visual representation of local TBS values) obtained from the analysis of a DXA image make up local and global data about the state of the bone microarchitecture. A low TBS value characterizes a bad microarchitecture (low connectivity, high intertrabecular spacing, low number of bone trabeculae); a high TBS values means a good microarchitecture high connectivity, low intertrabecular spacing, high number of trabeculae).
Analyzed DXA file: "hnr61mceq.dfs" (TBS analysis done on: 03/20/2012 14:22, version: 1.8.2.0M)

This report was based on the reanalysis of a DXA image. Before accepting this report, the user is held accountable for ensuring that the DXA examination has been carried out:
- by the osteodensitometer: 16082
- after the latest TBS iNsight calibration.

Med-Imaps TBS iNsight®

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